JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY

&

QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

*

VOLUME XVIII, NUMBER 1, JANUARY–MARCH, 1957

Published Quarterly by

MD PUBLICATIONS, Inc.

Félix Martí-Ibáñez, M.D., *President*

Editorial and Advertising Offices	*Circulation Offices*	
30 East 60th Street	1507 M St., N.W.	30 East 60th Street
New York 22, N. Y.	Washington, D. C.	New York 22, N. Y.

The Journal of Clinical and Experimental Psychopathology and Quarterly Review of Psychiatry and Neurology is published in March, June, September, December. The subscription rates are $11.00 per year; $28.00 for three years. Entered as second class matter at the Post Office at Washington, D. C., under act of March 3, 1879. Published by MD Publications, Inc., 1507 M Street, N.W., Washington, D.C.

PART I

JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY

ARTHUR M. SACKLER, M.D.
MORTIMER D. SACKLER, M.D.
Editors in Chief
The van Ophuijsen Center, New York, N. Y.

FÉLIX MARTÍ-IBÁÑEZ, M.D.
International Editor
Professor and Director of the Department of the History of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals, and The van Ophuijsen Center, New York, N. Y.

INTERNATIONAL RECORD OF CLINICAL AND RESEARCH PSYCHIATRY

The *Journal of Clinical and Experimental Psychopathology* was founded in 1939 by V. C. Branham, M.D., as the *Journal of Criminal Psychopathology*. In 1944 the title was changed to the *Journal of Clinical Psychopathology*; in 1951 the journal became the *Journal of Clinical and Experimental Psychopathology*. The present title (*Journal of Clinical and Experimental Psychopathology and Quarterly Review of Psychiatry and Neurology*) was assumed in 1954.

JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY

JANUARY–MARCH 1957

*

Clinical Psychopathologic Conferences are often included as a feature of the JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY. This section will attempt to further the elucidation of correlations and associations between clinical, neurologic, psychologic, and biologic elements. Clinical case presentations illustrative of psychophysiopathologic disorders will be gathered from psychiatric hospitals, clinics, and psychiatrists throughout the world. Manuscripts together with accompanying illustrations should be forwarded to the JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY, 30 East 60th Street, New York, N. Y., Attention: Editor, Clinical Psychopathologic Conferences.

QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

*

PSYCHIATRY ABSTRACTS

JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY
&
QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

*

Clinical Evaluation of Chlorpromazine Therapy for Mental Illnesses

Analysis of One Year's Experience

*Paul E. Feldman, M.D.**
TOPEKA STATE HOSPITAL
TOPEKA, KAN.

Thirty-seven physicians at the Topeka State Hospital undertook an evaluation of the therapeutic value of one of the new ataractic drugs, chlorpromazine.† For the past year these physicians have administered chlorpromazine to over 300 patients as therapy for various neuropsychiatric illnesses in order to determine the efficacy of the drug, its specificity if any, its optimum dosage, and the relationship between dosage and untoward effects. The following report summarizes the findings of these investigators.

STUDY METHOD

Data. Since this paper reports the findings of many physicians, it cannot reflect the variety of individual attitudes and responses nor the diversity of results and observations among the investigators. It was apparent, in analyzing the study data, that the physician's personal attitude toward the entire concept of pharmacotherapy for neuropsychiatric

* Director of Research and Education.

† The trade name of Smith, Kline & French Laboratories for chlorpromazine is Thorazine. Smith, Kline & French provided the chlorpromazine used in this study.

illnesses influenced his findings, even though all physicians used the same rating scales and criteria for judging treatment results.[1] Those investigators who began the study with few preconceptions of the value of drug therapy obtained results that, for the most part agreed with the findings of the group as a whole. As might be expected, physicians who entered the study with definite convictions about the drug's value showed the greatest range of results. On the one hand is the investigator who was predisposed toward drug therapy. One such physician found chlorpromazine effective therapy for 34 of his 44 pa-

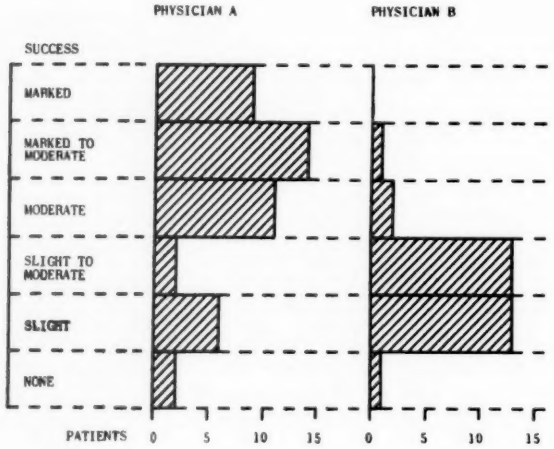


FIG. 1. Physician treatment success profiles.

Composition of Series

Diagnosis	Physician A (44 patients)	Physician B (30 patients)
Schizophrenics	29	26
Chronic brain syndromes	10	4
Involutional reactions	5	0

Patient data	Average years	Average years
Age	51	43
Duration of illness	12	10
Duration of hospitalization	9.5	5

Improvement	Patients %	Patients No.		Patients %	Patients No.	
Marked	20.5	9	77.5%	0	0	10%
Moderate to marked	32.0	14	34 patients	3.0	1	3 patients
Moderate	25.0	11		7.0	2	
Slight to moderate	4.5	2		43.0	13	
Slight	13.5	6		43.0	13	
None	4.5	2		3.0	1	

tients (physician A, fig. 1). Considering the long-term illnesses of his patients, their refractiveness to previous therapy, and the other factors for poor prognoses, this rate of success is no small accomplishment. On the other hand is the physician who rejected the concept of drug therapy for mental illness. One such physician found chlorpromazine effective therapy for only 3 of his 30 patients (physician B, fig. 1) despite their slightly more favorable prognostic factors.

It is from this variety of findings that this report derives its value of not being excessively colored by either favorable or unfavorable results obtained by a single investigator whose personal attitude toward drug therapy might influence his results.

Selection of Patients. Three hundred and twenty-one patients were selected to make up a test group typical of the population of the average state hospital. The group was composed of patients exhibiting schizophrenic reactions, chronic brain syndromes, manic-depressive reactions, involutional psychotic reactions, behavior disorders of childhood, psychoneuroses, and mental deficiency with psychosis (table I).

These patients were selected for the following reasons: (1) Failure to respond to other forms of therapy (electroconvulsive therapy, insulin coma, milieu therapy, psychotherapy). (2) Major problems in management (combativeness, hyperactivity, extreme negativism, bizarre autistic behavior). (3) Poor prognosis (long period of hospitalization, markedly regressive features, failure to show any change for the better for substantial periods of time). (4) Progressively downhill course. (5) Failure to maintain a gain derived from some other form of therapy.

It is self-evident that this group of psychotics—mainly schizophrenics—with an average age of 46½ years and an average time of hospitalization of nine years, who were chosen for the study because of the very poorness of their prognoses, is not a group to lead to overoptimism in terms of their potentialities for rehabilitation.

Dosage and Method of Administration. No specific instructions were issued as to maximum or minimum daily dosage, method and route of administration, frequency of administration, relationship to meals, etc., since the study was structured to obtain data on a variety of methods. Consequently dosages varied from 30 mg. to 2500 mg./day and were administered orally, intramuscularly, and intravenously. In some instances, multiple routes were used.

Fourteen patients received a combination of chlorpromazine and reserpine. Three of these 14 patients had failed to respond to either chlorpromazine or reserpine alone. Seven of them on combined therapy received a maximum daily dosage of 150 mg. of chlorpromazine and 1.5 mg. of reserpine.

Therapy Observations and Precautions. Patients were carefully observed for signs and symptoms of untoward reactions to chlorpromazine therapy. Hypotension, blood changes, and jaundice were looked for in particular. Blood pressure readings were taken frequently, and to prevent possible acute collapse, each patient was given bed rest for one hour following medication. This precaution was abandoned after a week because of the low incidence of hypotensive side effects (see Discussion). In the event that blood changes should occur as a result of therapy, blood studies were run on all patients. At the beginning of the study

TABLE 1
Study Group

	No. of patients	Per cent of entire group	Average age in years	Sex		Average duration (in years) of		Results of previous somatic therapy																
								Insulin					Electroconvulsive therapy					Lobotomy							
				M	F	Hospitalization	Illness	0	*	†	‡	§	0	*	†	‡	§	0	*	†	‡	§			
Schizophrenic reactions (238 patients)		74.0	43	72	166	8.5	11.5																	
Paranoid	87		43.5	25	62	6.5	10.0	15	4	2	1	2	25	4	3	2	4	5	—	—	—	—		
Catatonic	70		42	28	42	12.5	12.5	15	2	—	1	1	26	5	2	1	3	1	—	—	—	—		
Undifferentiated	50		44	9	41	10.0	13.0	4	1	2	—	—	10	—	1	—	1	—	—	—	—	—		
Hebephrenic	14		45.5	4	10	16.0	18.0	2	—	—	—	—	4	1	—	—	—	—	1	—	—	—		
Schizoaffective	10		38	2	8	4.0	7.0	2	—	—	—	1	2	—	1	—	1	—	—	—	—	—		
Catatonic with paranoid features	4		38	1	3	4.0	6.0	—	1	—	—	—	2	—	—	—	—	—	—	—	—	—		
Childhood type	1		15	1	—	2.5	2.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Simple type	2		40	2	—	8.0	12.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Chronic brain syndromes (42 patients)		13.0	63	18	24	4.0	7.0																	
Senile	18		74.5	9	9	5.5	6.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Arteriosclerotic	8		68	1	7	2.5	3.5	—	—	—	—	—	1	—	1	1	—	—	—	—	—	—		
Other types	16		49.5	8	8	3.5	9.0	—	—	—	—	—	1	—	1	—	—	—	—	—	—	—		
Manic-depressive reactions	14	4.4	65	8	6	11.0	14.0	—	—	—	—	—	—	1	3	1	2	—	—	—	—	—		
Involutional psychotic reactions	9	2.9	64	2	7	7.5	10.0	—	—	—	—	—	5	—	1	1	—	—	—	—	—	—		
Behavior disorders of childhood	2	0.7	14.5	2	—	1.5	3.0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Psychoneuroses	6	1.9	41	—	6	0.5	3.0	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Mental deficiency with psychosis	10	3.1	36	4	6	10.5	14.0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Total	321	100.0	46.5	106	215	9.0	10.5	39	8	4	2	4	76	11	13	6	11	6	1	—	—	—		

0 = No change.
* Determinable change in one area only, unsupported by other changes or not sustained.
† Fair improvement, affecting one area markedly or more than one area to some considerable degree.
‡ Good improvement in several areas, with marked changes in mental status but still insufficient for convalescent status.
§ Convalescent status, or its equivalent, permitted to go home under criteria of the hospital.

these tests were made at least once every two weeks. This policy was soon modified because few patients showed blood changes, and for the remainder of the evaluation one study was made every four weeks (see Discussion).

Concomitant Therapies. As a rule, no pre-existing program of therapy was discontinued. Patients were continued in psychotherapy or milieu therapy, and in many cases, the observations of clinical evaluators were augmented by reports from the ancillary therapists. As a result, we were able to evaluate the effect of chlorpromazine therapy upon electroconvulsive or insulin coma therapies, and even upon the necessity for seclusion or restraint.

Method of Evaluation. Previous writers have commented on the "highly variable and very individualized" responses to chlorpromazine and have noted that there was "little uniformity in degree or quality of therapeutic response."[2] For this reason a horizontal study was designed to assess the following items: hallucinations; hyperactivity; combativeness; negativism; orientation; appetite; accessibility; judgment; dress; memory; delusions; hostility; sleep; insight; affect; tension; appropriateness of conversation; bizarre mannerisms; realistic planning; self-mutilation; sociability; compulsiveness; amicability; participation in adjunctive therapy.

Individual observers, utilizing a four point scale (no—slight—moderate—marked improvement), rated their patients on each of these items. Items that were not applicable to a given patient were not rated in the evaluation so that a rating of "no improvement" in any of the 24 categories implies that the patient had some deficiency that failed to respond in some degree to chlorpromazine therapy. A minimal but clinically perceptible improvement in any category would be indicated by "slight" improvement, and complete amelioration of the symptomatology pertinent to any one of the above 24 items would be indicated by "marked" improvement. Some degree of change for the better that was in excess of "slight" but not to the extent of "marked" was indicated by "moderate" improvement. No evaluations have been included in this report that are not based on at least two months of continuous medication. Most of the patients had received chlorpromazine for from four to seven months at the time of evaluation.

After having been rated for improvement in each of the above categories, patients were evaluated for over-all degree of general improvement according to a six point scale (no—slight—slight to moderate—moderate—moderate to marked—marked improvement). This final evaluation was arrived at by a consensus of the evaluations of the individual items. A preponderance of "slight" improvement in the various categories indicated an over-all slight improvement; if most of the individual evaluations were "slight" with an occasional "moderate" or "marked" improvement in one or two categories, the over-all evaluation was recorded as "slight to moderate" improvement, etc. Many individual reports that were rated as "slightly improved" or "markedly improved" might have been rated otherwise by another observer. As a result, the findings in any individual case are not significant, but the mean result of 321 cases may be statistically significant.

STUDY RESULTS

Dosage. Adequate therapeutic effects with chlorpromazine appeared at a dosage of be-

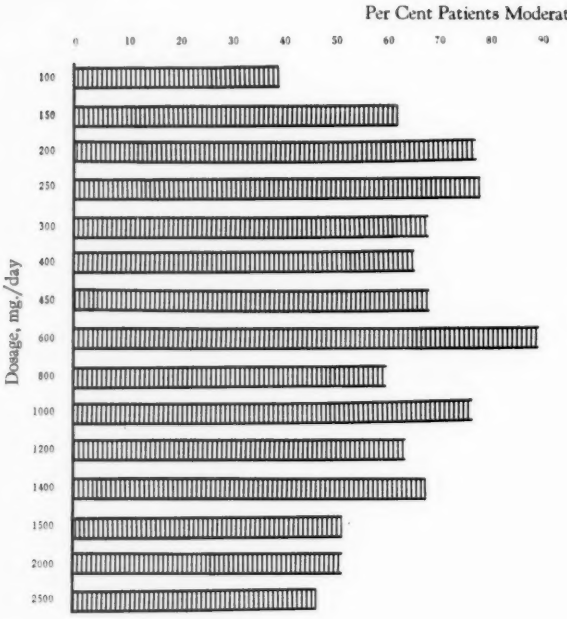


FIG. 2. Patient improvement at various dosage levels of chlorpromazine.

tween 200 and 250 mg. of the drug per day (fig. 2). From that dosage on, a plateau of efficacy was maintained regardless of further increases in the amount of medication given.

There did not seem to be any significant difference in therapeutic effect with various methods of administration. Most investigators appeared to prefer a divided dose administered three times daily. For a rapid therapeutic effect, some physicians prescribed chlorpromazine intramuscularly three times a day—others preferred to increase the dosage frequency to hourly intervals provided there was no excessive hypotensive response. A considerable amount of pain attended the intramuscular route of administration, but this was minimized by diluting the chlorpromazine with water, saline, or procaine, injecting slowly, and using multiple sites for succeeding injections, as recommended by Lehmann and Hanrahan.[3] Almost without exception, all physicians developed a preference for a gradual increase in dosage to the therapeutic optimal with a 50 to 100 mg. increase every three to seven days.

Our findings failed to show any consistent pattern of maintenance dosage once some degree of improvement had been attained. Some patients were unable to tolerate the least reduction in medication without undergoing some degree of relapse. It appears that this group of patients will have to be maintained indefinitely at their original therapeutic dosage level. Other patients, having attained a satisfactory improvement, were tapered off to 25 to 100 mg./day without suffering any regression. Eleven patients have been "weaned"

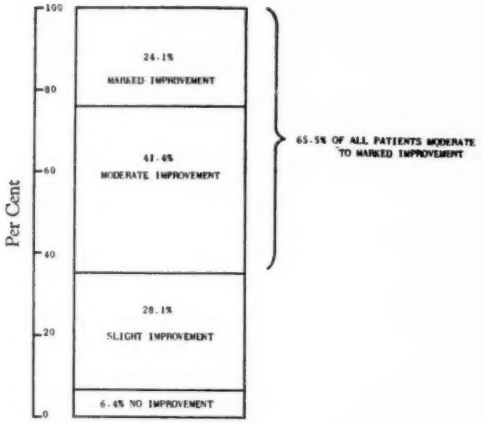


FIG. 3. Percentages of patients improved in entire group treated.

completely from the drug and have been without chlorpromazine from four to seven months without any evidence of relapse.

Chlorpromazine and Reserpine in Combination. The 14 patients who received a combined chlorpromazine-reserpine therapy were all rated as moderately or markedly improved even though 3 of these patients had failed to respond to one drug when administered alone.

General Therapeutic Responses. Of the patients in our series, 24.1 per cent showed "marked" improvement. An additional 41.4 per cent showed "moderate" improvement. Thus, chlorpromazine therapy has produced "moderate" to "marked" improvement in 65.5 per cent of our patients (fig. 3). To effect this substantial degree of improvement in approximately two thirds of our chronically ill patients has been a most gratifying experience. Equally gratifying is the finding that despite the initially poor prognoses for most of the patients, only 6.4 per cent failed to derive some benefit from chlorpromazine therapy. When analyzed, it appears that not all types of neuropsychiatric illnesses respond equally as well.

TABLE II

Results of Chlorpromazine Therapy for 238 Patients with Schizophrenic Reactions

Diagnosis	Improvement (percentages of patients)						Percentage of patients marked to moderate improvement
	None	Slight	Slight to moderate	Moderate	Moderate to marked	Marked	
Paranoid	4.5	13.0	23.0	20.0	28.0	11.5	59.5
Catatonic	2.5	21.5	20.0	20.0	27.5	8.5	56.0
Undifferentiated	10.0	26.5	28.5	14.0	21.0	0	35.0
Hebephrenic	7.5	7.5	50.0	14.0	21.0	0	35.0
Schizoaffective	0	30.0	10.0	10.0	0	50.0	60.0
Total all schizophrenic reactions	5.5	18.5	24.0	17.5	25.5	9.0	52.0

TABLE III
Duration of Illness and Degree of Improvement

Duration of illness (years)	Percentage of patients moderate or marked improvement
0–1	83.0
1–2	68.0
2–5	58.5
5–10	41.0
More than 10	52.0

Schizophrenic Reactions. Of our total group of 238 schizophrenic patients, 9 per cent achieved "marked" improvement, 25.5 per cent "moderate to marked" improvement, and 17.5 per cent "moderate" improvement, for a total of 124 patients (52 per cent) showing moderate to marked improvement as a result of chlorpromazine therapy (table II). Patients with paranoid or catatonic reactions responded best with 59.5 per cent and 56.0 per cent, respectively, of "moderate" to "marked" improvement. Table II indicates that 11.5 per cent of the paranoid reactions showed marked improvement, 28 per cent moderate to marked improvement, and 20 per cent moderate improvement. The catatonic reactions showed 8.5 per cent markedly improved, 27.5 per cent moderately to markedly improved, and 20 per cent moderately improved. Hebephrenic and undifferentiated reactions were benefited to a lesser degree. None of these patients achieved marked improvement, 21 per cent were moderately to markedly improved and 14 per cent were moderately improved, for a total of 35.0 per cent marked to moderate improvement. Although the 10 patients showing schizoaffective reactions comprise too small a group to warrant any generalizations, it should be noted that all patients with this diagnosis showed some improvement; over half were markedly improved.

Chronicity of illness was an important factor in the effectiveness of chlorpromazine therapy in the treatment of patients with schizophrenic reactions. As seen in table III, the shorter the term of illness, the more beneficial chlorpromazine therapy proved to be. The factors involved in our relative lack of success in the 5 to 10 year group are still unclear to us.

MANIC-DEPRESSIVE REACTIONS. Seven of 9 patients in a manic phase showed "moderate" or "marked" improvement, whereas but 1 of 3 patients in the depressed phase showed a

TABLE IV
Results of Chlorpromazine Therapy for 14 Patients with Manic-Depressive Reactions

	Improvement	Number of patients
Manic phase	None	0
	Slight	2
	Moderate	1
	Marked	6
Depressed phase	None	0
	Slight	2
	Moderate	1
	Marked	0

TABLE V

Results of Chlorpromazine Therapy for 9 Patients with Involutional Psychotic Reactions

Improvement	Number of patients
None	0
Slight	1
Moderate	3
Moderate to marked	3
Marked	2

moderate improvement (table IV). In several of our manic-depressive patients, typical cycles of mania that had been recurring in definite, predictable time patterns were disrupted by chlorpromazine and major breakdowns averted or ameliorated.

INVOLUTIONAL PSYCHOTIC REACTIONS. Our small series of 9 patients showed a most encouraging response to chlorpromazine therapy. Only 1 patient failed to show at least moderate improvement (table V). Three of these patients have been separated from the hospital, and an additional 3 will leave in the near future.

PSYCHOSIS WITH MENTAL DEFICIENCY. Our series consisted of but 10 patients, and their responses to chlorpromazine cover the entire range of the six point scale. Two of these patients have been released from the hospital and a third has recovered sufficiently to be awaiting transfer to a training school.

PSYCHONEUROSES. Four of the 6 psychoneurotics who presented anxiety to a disabling degree showed definite improvement under chlorpromazine therapy. Of the remaining 2 patients with this diagnosis, 1 showed no change and the other appeared to be definitely the worse for the medication.

ORGANIC BRAIN SYNDROMES. This group of 42 patients includes 26 patients with chronic brain syndromes associated with cerebral arteriosclerosis or senile brain disease and 16 patients with chronic brain syndromes associated with trauma, meningoencephalitis, convulsive disorder, Pick's disease, Alzheimer's disease, and alcohol intoxication. None of the senile dementias attained marked improvement, 22.0 per cent showed moderate to marked improvement, and 22.0 per cent showed moderate improvement, for a total of 44.0 per cent showing moderate to marked improvement. Of the arteriosclerotics, 25.0 per cent showed marked improvement, 25.0 per cent showed moderate to marked improvement, and 12.5

TABLE VI

Results of Chlorpromazine Therapy for 42 Patients with Organic Brain Syndromes

Diagnosis	Improvement (percentages of patients)						Percentage of patients marked to moderate improvement
	None	Slight	Slight to moderate	Moderate	Moderate to marked	Marked	
Senile	22.0	16.5	16.5	22.0	22.0	0	44.0
Arteriosclerotic	12.5	25.0	0	12.5	25.0	25.0	62.5
Other types	7.0	30.5	30.5	12.5	12.5	7.0	32.0
Total all organic brain syndromes	14.0	24.0	19.0	16.5	19.0	7.5	43.0

TABLE VII

Degree of Improvement in Criteria-of-Evaluation Factors (Total Study Group)

Factor	Degree of improvement (percentages of patients)				
	Marked	Moderate	Slight	None	Total marked or moderate benefit
Insight	2.5	9.5	22.0	66.0	12.0
Judgment	7.5	15.0	26.0	51.5	22.5
Memory	5.5	23.0	28.0	43.5	28.5
Orientation	9.5	20.5	32.0	38.0	30.0
Realistic planning	12.0	19.0	20.0	49.0	31.0
Affect	12.5	21.0	31.5	35.0	33.5
Compulsiveness	16.0	18.0	22.0	44.0	34.0
Self-mutilation	23.5	19.5	24.5	32.5	43.0
Participation in adjunctive therapy	22.5	21.0	32.0	24.5	43.5
Sociability	17.5	26.5	34.0	22.0	44.0
Appropriateness of conversation	19.0	28.5	31.0	21.5	47.5
Delusions	21.0	27.0	26.0	26.0	48.0
Dress	18.0	30.5	34.0	17.5	48.5
Appetite	21.5	29.5	34.5	14.5	51.0
Amicability	19.0	34.5	31.5	15.0	53.5
Accessibility	24.5	29.0	31.0	15.5	53.5
Mannerisms	28.5	26.0	20.0	25.5	54.5
Sleep	28.0	27.5	28.0	16.5	55.5
Negativism	29.0	28.5	32.0	10.5	57.5
Hallucinations	30.5	27.5	21.0	21.0	58.0
Hostility	33.0	34.0	23.0	10.0	67.0
Tension	29.0	42.0	18.5	10.5	71.0
Hyperactivity	38.0	35.0	20.5	6.5	73.0
Combativeness	49.0	25.0	15.0	11.0	74.0

per cent showed moderate improvement, for a total of 62.5 per cent showing moderate to marked improvement. Of the miscellaneous group, 7.0 per cent showed marked improvement, 12.5 per cent moderate to marked improvement, and 12.5 per cent moderate improvement, for a total of 32.0 per cent showing moderate to marked improvement. Quite a few chronic brain syndrome patients showed surprising improvement in areas such as memory, judgment, orientation, etc., which are areas in which we ordinarily presume that the defect represents an organic deficit.

The entire group of chronic brain syndrome patients showed 7.5 per cent markedly improved, 19.0 per cent moderate to markedly improved, and 16.5 per cent moderately improved, for a total of 43.0 per cent showing moderate to marked improvement. This has added significance in that it appears that chlorpromazine may eliminate or ameliorate those symptoms that may have prevented boarding-home or family placements. Agitation, destructiveness, excitement, irritability, insomnia, confusion, and all the other symptoms that make incarceration of the aged advisable all responded well to chlorpromazine. Ease of management was consistently reported by nursing personnel. In our series, 5 patients (12 per cent) have been placed outside of the institution and another 6 are in the process of separation.

Response Evaluations. A variety of successes were encountered in dealing with the spe-

cific items listed under "Method of Evaluation." The results of this evaluation are given in table VII in the order of increasing effectiveness of response to chlorpromazine therapy.

INSIGHT. The response of this category was most disappointing; only one third of our patients improved in this area. An occasional over-all dramatic improvement was associated with an equally dramatic improvement in insight, but many very satisfactory improvements did not show this associated change. JUDGMENT. No assessment could be made of the prepsychotic judgment of the patients, but it was assumed (probably erroneously) that the judgment of patients prior to breakdown was adequate. Of our patients, 234 displayed some defect in judgment before medication. Following medication less than one half showed improvement. Many patients who showed dramatic clinical improvement failed to show a corresponding improvement in judgment. MEMORY. One hundred and twenty of our patients showed some defect in recent or remote memory prior to receiving chlorpromazine therapy. Fifty-six per cent showed some improvement following therapy, with 5 per cent showing complete return of memory. ORIENTATION. Before therapy, 150 patients presented some defect in one, two, or three of the categories of time-place-person. No attempt was made to study any particular defect of orientation, and all patients were considered in a single group. Sixty-two per cent responded in some degree, and a small fraction (9.5 per cent) showed complete restoration of orientation. Improvements noted were not limited to patients classified as having functional disorders; many patients with organic brain syndromes showed surprising improvement.

REALISTIC PLANNING. Although there was improvement noted in over half of the patients treated, few displayed the sort of realistic planning for their future, both in or out of the hospital, that we would like to see. AFFECT. Almost two thirds of the 242 patients who originally showed a defect in affect (inappropriateness, shallowness, blunting, etc.) improved to some degree. COMPULSIVENESS. As might be expected from a mechanism that has as one of its primary purposes the reduction of anxiety, compulsiveness did not respond as well to chlorpromazine therapy as some of the other defects. We found that over half of our patients showed some improvement in this area. SELF-MUTILATION. Included in this category are the deliberate attempts at destruction of part or parts of the body as well as the injurious effects incidental to stereotyped behavior (face-rubbing, fist-pounding, etc.). Of the patients treated, 67.5 per cent showed improvement in this category. PARTICIPATION IN ADJUNCTIVE THERAPY. The improvement in such areas as amicability, sociability, hostility is reflected in the increased participation that was witnessed in adjunctive therapy. On one of the wards where a blind controlled study of chlorpromazine was carried out,[4]

TABLE VIII

Improvement in Accompanying Affect among 74 Patients with Delusions Unimproved or Slightly Improved by Chlorpromazine Therapy

Improvement	Number of patients	Per cent of patients
None	23	31.0
Slight	35	47.0
Moderate	13	17.5
Marked	3	4.5

patient participation in adjunctive therapy increased from 4 to 5 patients per session to 12 to 15. Our over-all results in this area show that 75.5 per cent of the patients improved somewhat in participation (43.5 per cent improved moderately to markedly). SOCIABILITY. Seventy-eight per cent of our patients were noted as becoming more sociable as judged by their increased participation in adjunctive therapy activities, recreation, and various forms of social activity. APPROPRIATENESS OF CONVERSATION. In this area, 78.5 per cent of the patients showed improvements in relevance of speech, rational ideation, and other aspects of communication. DELUSIONS. Two hundred and one patients with delusions were studied to see to what extent the delusions were ameliorated or eliminated by chlorpromazine therapy. In our series we refer specifically to the actual elimination of delusions (of both recent and remote origin), and it appears that almost half of the patients showed moderate to marked improvement. In many patients the improvement was most striking and dramatic. In an effort to evaluate the fate of the accompanying affect, a further study was made of 74 patients who showed only slight or no improvement in their delusions. As seen in table VIII, few showed any significant improvement in accompanying effect.

DRESS. Under this category were considered such factors as habits of personal hygiene, attention and interest in attire, effort made by the patient to maintain a neat appearance, general traits indicating slovenliness or meticulousness, and the degree of orderliness of personal possessions. In 238 patients in our series there appeared to be some defect in this area at the start of the therapy program. At our last analysis 196 patients (82.5 per cent) showed some improvement. In this respect, chlorpromazine must be considered a most effective drug. It apparently operates by diminishing regressive tendencies, by increasing interest in self and environment, by relieving patients from pressures of preoccupation, and by the many other factors that enter into this sphere. In a few patients, this was the only area evaluated that appeared to have changed for the better. Although these patients showed little or no improvement in antisocial behavior, delusional systems, or destructive tendencies, it was quite obvious that they had undergone some improvement, either in their habits of hygiene or in personal dress. In fact, chlorpromazine was administered to 1 patient only because of her destructive attitude toward her clothing. While the patient was under the influence of the drug, this behavior was completely eliminated.

APPETITE. Any degree of anorexia or refusal to eat because of negativism, delusions, or pressure of activity was considered to be a defect in "appetite." At the start of the study, 149 patients demonstrated such a defect. Following the administration of chlorpromazine, 85 per cent of these patients showed a definite improvement in their intake of food. A gain in weight was a usual concomitant of improvement in other areas, but, occasionally, appetite improvements (sometimes to the degree of voraciousness) were witnessed without improvement in the mental state. AMICABILITY. Eighty-five per cent of the patients given chlorpromazine became more amicable. That is, not only did they show a loss of hostility, but they demonstrated a willingness and tendency to indulge in friendly, interpersonal relationships, and often a tendency or willingness to engage in the group relationships included under "sociability."

ACCESSIBILITY. This category refers to the ability of the patient to be "reached" by the

therapist. There is the implication of an ability to comprehend the nature of the therapeutic maneuver from the standpoint of both reception and the ability to verbalize thoughts, conflicts, delusional systems, etc. Many of our patients who had been mute for years, or who had refused to verbalize their thoughts during an interpersonal relationship, became amenable to all sorts of psychotherapeutic procedures. Improvement was recorded in 84.5 per cent of the 249 patients who originally were inaccessible. MANNERISMS. One hundred and forty-five of our schizophrenics displayed characteristic mannerisms. In some patients the behavior was disabling (but not mutilative or compulsive); in other patients it was an incidental finding. Our results show that 108 (74.5 per cent) of these patients exhibited some improvement under chlorpromazine therapy. SLEEP. Patients included in this group were those who required some degree of sedation before sleep was possible and those who spent some portion of the night roaming the ward and disturbing other patients. Perhaps one of the most satisfying effects of chlorpromazine has been its ability to provide natural sleep without the necessity for auxiliary medication. Of our patients, 83.5 per cent showed this improvement. Some of our patients became somnolent during the day, but this did not appear to interfere with the night sleep cycle.

NEGATIVISM. Negativism was taken to include the usual phenomena of resistiveness to various routines (therapeutic, hospital, and administrative), lack of cooperation, refusal to comply with orders or suggestions, etc. Two hundred and fifty-seven patients originally manifested some degree of negativism; following an adequate therapeutic trial with chlorpromazine, well over half of them responded, 89.5 per cent showing some improvement. This effect of chlorpromazine has tremendous implications in terms of increased ease and flexibility of patient management and therapy. It appears quite definitely that chlorpromazine is a most potent drug for the relief of this disabling symptom.

HALLUCINATIONS. One hundred and nineteen patients were studied in this aspect of the investigation. Our experience has been that hallucinations respond more readily to chlorpromazine therapy than do delusions; 94 patients (79 per cent) had a good response to the therapy in that their hallucinations were completely eliminated or were moderately to markedly reduced in intensity and frequency. A study of the accompanying effect was made comparable to that made for delusions. It reveals essentially the same sort of findings; the accompanying affect responds only slightly or moderately in most patients in whom the hallucinations are not reduced (table IX).

HOSTILITY. Under hostility were included all manifestations of aggressiveness other

TABLE IX

Improvement in Accompanying Affect among 38 Patients with Hallucinations Unimproved or Slightly Improved by Chlorpromazine Therapy

Improvement	Number of patients	Per cent of patients
None	8	21
Slight	19	50
Moderate	10	26
Marked	1	3

TABLE X

Effectiveness of Chlorpromazine Therapy by Chronicity of Illness (All Patients)

Duration of illness (years)	Number of patients	Improvement			
		None (%)	Slight (%)	Moderate (%)	Marked (%)
0–1	13	0	23.0	23.0	54.0
1–2	20	0	20.0	50.0	30.0
2–5	70	1.5	31.0	33.0	34.5
5–10	60	8.4	21.6	55.0	15.0
More than 10	155	8.5	31.5	40.0	21.0

than overt combativeness. Two hundred and twenty-six patients in our series showed this trait before chlorpromazine therapy; 203 of them improved following medication. This category does not appear to score quite as well as "hyperactivity" but still indicates that a very respectable number of the patients (90 per cent) showed some improvement in this area. HYPERACTIVITY. The usual clinical phenomena associated with an increased tempo of action and ideation are remarkably affected by chlorpromazine. In some of our patients a reduction in hyperactivity seemed to be associated with the hypnotic effect of the drug, but in most cases this effect was not present. The number of patients helped by the drug—180 of 193 (93.5 per cent)— is quite significant. Chlorpromazine's ability to lessen hyperactivity is one of the important benefits that contributed to the drug's over-all efficacy in improving the general condition of patients. COMBATIVENESS. Before therapy, 168 of our patients were overtly combative. The response of this type of patient to chlorpromazine is most dramatic; only 19 patients failed to show any improvement after receiving the drug. In a very substantial portion of our patients this behavior was virtually eliminated. This resulted in a diminution of tension on the wards and an improvement in interpersonal relationships. TENSION. Tension included various manifestations of anxiety such as psychomotor restlessness, apprehensiveness, tremulousness, agitation, etc. Eighty-nine per cent of the patients treated for these symptoms were relieved to some degree by chlorpromazine.

Chronicity of Illness. Chlorpromazine was found most effective in treating patients who had been ill but a short time. Almost 79 per cent of the patients ill for less than two years showed at least moderate improvement, almost 40 per cent showing marked improvement. More significant is chlorpromazine's ability to do some good at all stages of chronicity. Of the patients who had been ill for longer than 10 years, 61.0 per cent responded favorably, over 21 per cent showing marked improvement (table X).

UNTOWARD EFFECTS

Twenty-one different side effects were noted in 135 of our patients (42 per cent). In other words, almost half of the patients in the study exhibited one or more undesirable or unintended reactions to chlorpromazine therapy. However, as seen in table XI, the incidence of many of these side effects was not significant.

Depression. Seven patients (2.2 per cent) in our series developed an untoward depression.

In 4 of these patients the depression was eliminated by discontinuing medication. One patient showed a good response when electroconvulsive therapy was administered without stopping medication. There were 2 suicides in our series; neither patient, however, appeared to be in overt depression even though the manner of death indicated considerable premeditation in both patients. There were no indications that might have alerted personnel. There is also no evidence to relate the suicides to the medication; indeed, 1 of the patients had tried to commit suicide in a similar manner four years prior to receiving chlorpromazine; the method he used then was identical to the one that succeeded. The incidence of depression was too low to warrant any conclusions as to whether it is a low or high dosage manifestation. This side effect occurred throughout the range of dosages, from 200 to 750 mg./day. Despite the low incidence of depression and suicide, the serious nature of this untoward effect precludes any possibility of complacency in the chlorpromazine therapy regimen.

Drowsiness. The most common side effect noted was drowsiness. At times, however, we considered it an asset rather than an untoward effect, especially when it contributed to the tranquilization of hyperactive patients. Occasionally, when it interfered with other forms of therapy (adjunctive, industrial, or psychotherapy), drowsiness was definitely detrimental. In most cases, drowsiness did not persist for more than 7 to 10 days. The degree of drowsiness was most unpredictable; in some patients it was so mild as to be negligible; in others it was so profound that it was necessary to prescribe cerebral stimulants to combat it. The most effective stimulant was a moderate dose of 5 to 10 mg. of Dexedrine, which eliminated the drowsiness without destroying the desirable effects of chlorpromazine.

Usually the side effect disappeared spontaneously or could be eliminated by reducing the dosage. In exceptional cases the drowsiness was so severe and persistent that it interfered with the total treatment program, and these few patients had to be taken off the drug.

TABLE XI
Incidence of Side Effects

Side effect	Number of patients	Percentage of patients
Drowsiness	73	22.8
Parkinsonism	12	3.8
Skin rash	12	3.8
Dizziness	9	2.8
Hypotensive response	9	2.8
Depression	7	2.2
Jaundice	6	1.9
Blood changes	6	1.9
Vomiting	6	1.9
Turbulence	6	1.9
Weakness	3	.9
Seizures	3	.9
Edema	3	.9
Increased salivation	2	.6
Visual disturbances	2	.6
Amenorrhea	2	.6
Constipation	2	.6
Confusion	1	.3
Urinary retention	1	.3
Bradycardia	1	.3

In our experience, the maximum incidence of drowsiness appears when chlorpromazine is administered in doses of 250 to 600 mg./day. Above and below this dosage level, there is relatively little drowsiness produced.

Parkinsonism. Whereas drowsiness seemed to be a middle-dose phenomenon, parkinsonism appears to be a manifestation of high dosages. The appearance of a parkinson-like state did not seem to affect our patients either favorably or adversely. Other than for some mild physical limitations, it did not interfere with the rehabilitative program and rarely required medication.

Skin Rash. In comparison with the reports in the current literature, we experienced a low incidence of skin rashes (3.8 per cent). In most instances it appeared to be a minor disorder with a moderate amount of pruritus which responded well to antihistaminics. In 3 patients, however, the disturbance was more severe and caused incapacitation. These patients did not respond to conservative management, and chlorpromazine was discontinued; however, the rash and pruritus persisted and were eliminated only after the patients were treated with cortisone. The appearance of a rash could not be correlated with the size of the dose but appeared to manifest itself at all of the various dose levels used with about the same frequency. We did not encounter any rashes in persons handling chlorpromazine.

Dizziness. Temporary dizziness occurred in 2.8 per cent of our patients. It could not be correlated with any particular dose level but occurred all along the therapeutic dosage scale.

Hypotensive Responses. We found that hypotension was a relatively infrequent side effect; only 2.8 per cent of our patients were affected. It did not interfere with the patients' routines, and in only 1 patient was the blood pressure drop of any consequence. No serious cardiovascular collapses were noted, even in the aged. The one patient who showed any notable drop in blood pressure collapsed within an hour of receiving 200 mg. of the drug. There was no loss of consciousness, and the patient quickly recovered following bed rest. Strangely, no hypotensive responses were reported in patients receiving in excess of 300 mg. of chlorpromazine per day. This seems to suggest that hypotension is a manifestation of low dosage.

Jaundice. We have had a most peculiar experience with this particular side effect. Early in the project, when our series was relatively small, and our attention was centered about the possible appearance of some evidence of icterus, we encountered as high as 10 per cent of jaundice in our patients. As our understanding of the involvement increased and its relative importance as an untoward effect was minimized, the incidence of jaundice began to fall, until at this time our total incidence is 1.9 per cent. I would suspect that our present incidence of jaundice in new therapy cases would prove to be about 1 per cent. No jaundice was reported at a dosage higher than 400 mg. of chlorpromazine per day. Apparently this side effect shows a disposition similar to that encountered with hypotension; that is, it occurs most frequently when low dosages of the drug are administered.

Other Side Effects. HEMATOLOGIC. Six patients (1.8 per cent) showed a significant drop in the number of white blood cells during the course of chlorpromazine medication. In no cases did there appear to be associated findings that would justify a diagnosis of agranulocytic angina. All of our cases promptly and uneventfully returned to normal when the

medication was discontinued. VOMITING. Six patients developed vomiting that was definitely related to chlorpromazine medication. All 6 were receiving 450 mg./day or less, and in all cases the vomiting subsided within a few days without discontinuance of medication. TURBULENCE. Six patients showed an increase in combativeness, hyperactivity, tension, and antisocial trends to such an extent that they had to be taken off chlorpromazine therapy before an adequate trial of the drug could be made. This side effect occurred at all dosage levels, from 150 to 800 mg. of chlorpromazine per day.

All other side effects showed an incidence of less than 1 per cent each. Of particular interest are 3 patients who showed unquestionable grand mal–type seizures although they had no previous histories of convulsive disorders. Indeed, 1 of these patients had a known normal electroencephalogram prior to chlorpromazine medication; when this patient was retested after the grand mal attack, the findings were reported as "pathologic."

In contrast to this effect of chlorpromazine therapy is the effect the drug had on 1 epileptic patient who was included in our study group. Prior to receiving chlorpromazine, this patient averaged one grand mal seizure every 7 to 10 days, but during the course of our study experienced but one seizure during a 12 week period.

Only 2 of our patients were reported to have developed amenorrhea, and there were no reports of lactation in any of the patients. One physician who did not participate in this study encountered an unusually high incidence of amenorrhea and an occasional lactation.

One patient receiving 150 mg. of chlorpromazine per day developed urinary retention that promptly subsided when medication was discontinued. Two patients reported blurring of vision that also subsided, but without discontinuance of medication. Constipation or diarrhea was occasionally encountered, as was dryness of the oral and nasal mucosa. The

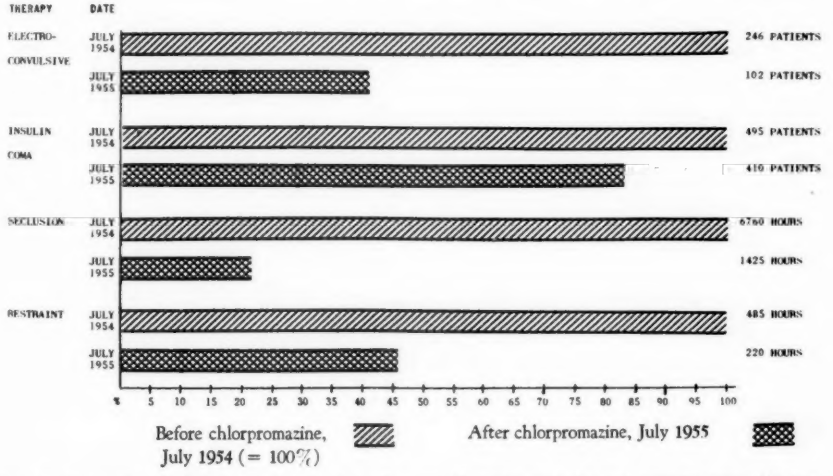
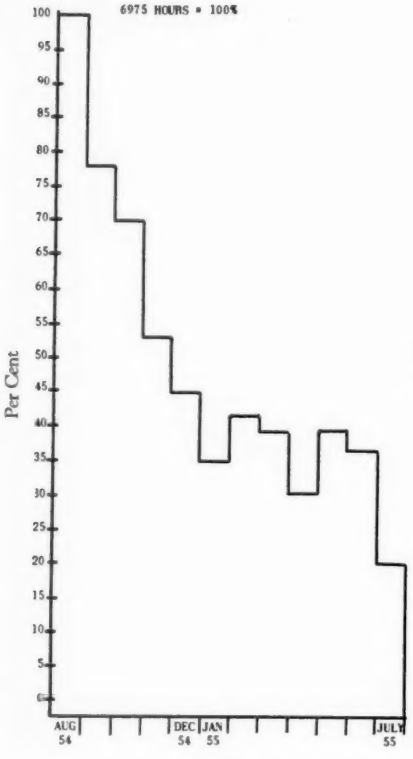


FIG. 4. Comparison of electroconvulsive and insulin coma therapies; seclusion and restraint rates July 1954 compared with July 1955 (July 1954 = 100%).



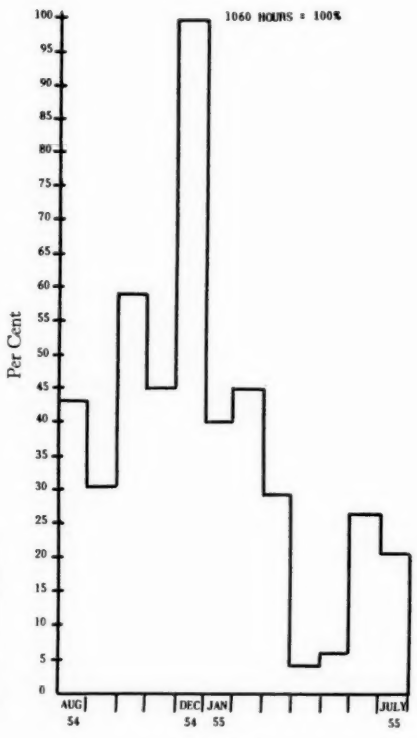


FIG. 5. (Left) Seclusion rate, August 1954 through July 1955. FIG. 6. (Right) Restraint rate, August 1954 through July 1955.

mucosal involvements were so infrequent and responded so readily to antihistaminics that they were not reported as side effects.

Electroconvulsive and Insulin Coma Therapies. July 1954 is the only month before chlorpromazine therapy was begun for which data are available on the number of patients given electroconvulsive or insulin coma therapies. It is interesting, although not necessarily significant, that in July 1955, after chlorpromazine had been given for a year, almost 60 per cent fewer electroconvulsive therapies and about 20 per cent fewer insulin coma therapies were given than in the same month before the chlorpromazine study was begun (fig. 4).

Seclusion and Restraint. Our data for seclusion and restraint include other factors besides the indications of hyperactivity, aggressiveness, etc. Data on seclusion include the hours spent in isolation by quiet and cooperative patients who wished added privacy or protection

from their own hostile impulses; data on restraint include the use of mechanical supports such as chest binders for feeble patients. Despite these broad bases for the data on seclusion and restraint, both rates have fallen during the year of the chlorpromazine study. A comparison of July 1954 with July 1955 shows that the number of hours of restraint was reduced by almost 80 per cent and of seclusion by almost 50 per cent (fig. 4). The reduction in the seclusion rate is most dramatic during the year of the study (fig. 5). In August 1954, the first month of the study, patients spent almost 7000 hours in seclusion; in July 1955, only about 1400 hours. The trend of the restraint rate (fig. 6), although not as clear-cut a descent as that of seclusion, is nevertheless a downward slope. Although there are many conjectures about why the use of physical restraint and mechanical support should have increased during the Christmas season (December, fig. 6), our data do not permit a definite explanation.

Lobotomies. Since the introduction of chlorpromazine, not a single lobotomy has been performed at the Topeka State Hospital. Prior to the introduction of the drug, a year ago, there had been a definite lobotomy program, which though on the decline, was still functioning. It is a reasonable presumption that the discontinuance of lobotomies has, at least in part, been due to the introduction of chlorpromazine. Several patients who had been approved for lobotomy and were awaiting surgery responded to chlorpromazine to the extent that the plans for surgery were abandoned.

Seven of the patients in our series had lobotomies prior to trial with chlorpromazine but had not responded favorably to this surgical procedure. After receiving chlorpromazine, 2 patients showed slight improvement, 1 slight to moderate improvement, 3 moderate improvement, and 1 of these patients showed moderate to marked improvement.

DISCUSSION

Dosage. There does not appear to be any standard dosage of chlorpromazine. Although our findings indicate that most patients respond to doses of between 200 and 250 mg. daily, there were patients who responded to as little as 30 mg./day, and others who required as much as 2500 mg./day to effect similar responses. Lehmann[5] considers an average minimum dose to be 100 to 300 mg. of chlorpromazine daily, and Cohen[2] places a minimum dose at 200 mg./day. These findings agree with ours. However, both believe that the upper level of clinically effective doses may be 800 mg. daily, over three times the upper limit we found generally effective. Probably too much emphasis is placed on the idea of "standard" or "average" dosage. As seen in figure 2, patients respond to all but the lowest dosage levels. For this reason, Cohen's observation[2] that the dosage has to be "individualized" on the basis of clinical response should be the guide for administering chlorpromazine.

It is interesting that some physicians, among them Moyer et al,[6] justify their use of large doses of chlorpromazine (2,000 to 4,000 mg./day) as an attempt to attain some degree of parkinsonism, which they feel is essential to a therapeutic effect. We could not confirm this belief. Our results with varying doses seem, instead, to support the contention of various writers that patients receiving 200 to 400 mg./day did not show any added improvement when dosages were raised to the vicinity of 2,000 mg./day. Moreover, we could not

find any correlation between the appearance of parkinsonism in a patient and his benefit from chlorpromazine therapy.

It was our unconfirmed impression that there may be some relationship between the duration of medication and the ability to withstand discontinuance of the drug. The literature is not definite on this point, although Winkelman[7] reports that there is no consistent relationship, and Goldman[8] believes that the more severe and prolonged the patient's psychotic involvement, the longer chlorpromazine will have to be administered before it can be withdrawn without a relapse. In our study it seemed that the longer a patient had received the drug, the more capable he became of tolerating a cessation (or reduction) of the medication.

Chlorpromazine and Reserpine in Combination. Our attention was called to this form of therapy rather late in our study. In all, only 14 patients received the combination. The excellent results in this small group—all patients moderately to markedly improved—are most suggestive and warrant further investigation. Lemere[9] reported that 66 per cent of his patients were helped by combined therapy, whereas only 49 per cent were helped by chlorpromazine and 46 per cent by reserpine. Tuteur,[10] reporting a similar study, does not indicate the relative success of combined therapy but comments on the advantages of combining the two drugs, namely, effectiveness of smaller dosage of each and the relative absence of side effects. All studies seem to find a dosage ratio of 1 mg. reserpine per 100 mg. chlorpromazine most effective. This ratio was used in our study and was found effective for all 14 patients.

General Therapeutic Responses. It is significant that 65.5 per cent of our patients showed "moderate" to "marked" improvement under chlorpromazine therapy. What is equally significant is that only 6.4 per cent of our patients failed to show some sort of response to the drug. Perhaps as our knowledge of how to use the drug increases, we may devise methods for improving the condition of those patients who failed to show more than slight improvement. It is interesting that when our year's study was but half completed, and our series consisted of 160 patients, 16.9 per cent of the group failed to show any improvement and an additional 20 per cent showed only slight improvement. This total of 36.9 per cent is essentially the same as our final figure of 34.5 per cent for patients who failed to show more than slight benefit from the therapy. However, the 16.9 per cent who had shown "no improvement" six months ago has been reduced to 6.4 per cent. The most likely explanation for this drop would appear to be that even in the intractable cases, if the medication is continued for long periods of time (four to six months), some changes for the better may ensue. The literature reveals widely divergent opinions on this point. Elkes and Elkes[11] feel that the full effect of chlorpromazine does not become apparent until after three to six weeks of continuous medication. Azima and Ogle,[12] on the other hand, feel that chlorpromazine will manifest its good effects within the "first few days."

To date, 41 patients have been released from the hospital and an additional 43 patients are in the process of separation. These release figures of 84 patients (26.5 per cent of the patients in the study) do not imply that these patients have been "cured." On the contrary, in very few instances did we feel that the patient was in complete remission. Those

released were discharged to themselves, paroled to their families, or transferred to boarding homes. In each case, however, the patient had benefited from chlorpromazine therapy so much that he was now able to withstand the pressures of life outside of an institution. In those patients who were transferred to boarding homes, the improvement may have been from untidiness to tidiness, from hostility to amicability, from insomnia to normal sleep patterns, etc. Many patients, although they had no improvement in memory, orientation, delusional systems, etc., had lost those attitudes and behaviors that prohibited boarding-home care or life within a community. As a result of the therapy they had received, they are now able to adjust quite well to their environments outside of the hospital.

Schizophrenic Reactions. Goldman[8] feels that chlorpromazine is a specific for schizo-affective reactions. Although our findings show that all of our patients with this diagnosis were benefited by chlorpromazine therapy, our small group of patients—only 10—is not large enough to warrant any such definite conclusion. However, our excellent results in treating patients for schizoaffective reactions do support Goldman's contention. In dealing with schizophrenic reactions as a whole, however, our findings do not agree with those given by Goldman, who found that 93 per cent of his schizophrenic patients attained either complete or social recovery or improved to the extent that they no longer required restraint, etc. This is a substantially higher "success rate" than we were able to attain. Our results show that only 63 per cent of patients with schizophrenic reactions were improved by chlorpromazine therapy. Lehmann[5] reported 61.3 per cent moderately or markedly improved, and Cohen[2] found that approximately 60 per cent of his 1000 patients showed reduction in intensity of symptoms to apparently complete resolution of illness. These, I believe, are more realistic figures than the 93 per cent given by Goldman. Our results, which agree with Cohen's and Lehmann's, were obtained in a group of schizophrenic patients who, for the most part, had failed to respond to other forms of therapy and had an average duration of illness of 8.5 years.

Manic-Depressive Reactions. Our excellent results with chlorpromazine therapy in treating patients for manic-depressive reactions are in keeping with numerous reports that show comparable results with larger series of patients than the 12 whom we treated. Lehmann and Hanrahan[3] and Moyer et al[6] believe chlorpromazine to be especially beneficial to patients with these diagnoses. Goldman[8] maintains that in "patients who show a great deal of initial excitement, particularly manic and schizo-affective disorders, [chlorpromazine] is practically specific." Delay and Deniker[14] state that "chlorpromazine has become the treatment of the manic episode, in the same way that electroshock has become the treatment of the depressive phase."

Although Lehmann's observation that "complete remission of manic phase within 40 days in 48 per cent of cases" is possible with chlorpromazine therapy, it is substantially lower than our results (78 per cent) with a more limited series; his observation[3, 5] that the drug disrupts cycles of mania and averts or ameliorates major breakdowns agrees with our findings.

TABLE XII
Ferguson Scale Variations

Clinical evaluation (improvements)	Variation in range of Ferguson Scale ratings (total score)
None	—1 to +2
Slight	—17 to +37
Slight to moderate	+6 to +11
Moderate	—8 to +65
Moderate to marked	—13 to +66
Marked	+51 to +66

Psychoneuroses. Our results in treating patients showing psychoneuroses agree with those reported by Winkelman,[7] who found that anxiety "was well controlled in the majority of cases exhibiting this symptom."

Organic Brain Syndromes. Chlorpromazine is especially useful for treating patients exhibiting organic brain syndromes because, as Lehmann[5] points out, it does not increase confusion. On the whole, our favorable results with the drug seem to corroborate those of Winkelman,[7] Sainz,[13] and others who found chlorpromazine of moderate or marked value in treating over 40 per cent of their patients. Our results are somewhat at variance with those given by Lehmann, who reported 66 per cent of senile patients moderate or markedly improved as against our findings of only 44 per cent with equal improvement.

Response Evaluations. During the course of our double-blind study,[4] a discrepancy was noted between the clinical evaluation of our patients and the results of Ferguson Scale rating. Because of this, 42 patients were evaluated by both methods. Our results indicated that these discrepancies persisted, and we can only conclude that the Ferguson Scale is not a reliable means of checking the tranquilizing drugs. The major differences were found in judging "slight," "moderate," and "moderate to marked" improvements (table XII).

The most conspicuous effect of chlorpromazine is its ability to lessen hyperactivity. Cohen[2] writes, "its capacity to convert highly disturbed behavior into docile tractability has remained an impressive phenomenon," and Lehmann[5] confirms this observation by saying, "the drug is of great clinical value for the symptomatic control of virtually any state of psychomotor excitement." Our statistics are very much in support of these observations.

Another outstanding achievement of chlorpromazine therapy is the lessening of tension in almost 90 per cent of the patients. Numerous writers have experienced similar success in treating this symptom. Winkelman,[7] in one of the earlier reports on the drug, writes of the "gratifying results" obtained in treating tension states; Lehmann and Hanrahan[3] find that "emotional tension is well controlled by comparatively small doses of 50 to 200 mg. daily;" and Cohen[2] reports excellent results in treating agitation and anxiety.

As seen in table VII, although chlorpromazine was of some help in improving almost all symptoms of mental illnesses, it was especially helpful in treating these two factors, hyperactivity and tension.

Untoward Effects. HYPOTENSIVE RESPONSES. When we began this study we anticipated that patients would develop important drops in blood pressure as a result of chlorpromazine

therapy. In fact, we had originally structured the study to include bed rest for one hour following each medication. This plan was abandoned within a week because the anticipated hypotensive responses did not appear. Hypotension remained an infrequent side effect that did not interfere with the patients' routines. Our experience with the hypotensive effects of chlorpromazine is supported by Goldman,[8] who, in a report on 500 patients, observes that "precautions noted in the European literature to avoid acute collapse from hypotension seem to be somewhat excessive since such reactions were extremely rare, even with larger dosage." We cannot account for the finding by Moyer et al[6] that "hypotension occurred in all but a few cases" or that of Azima and Ogle[12] that moderate hypotension occurs in 90 per cent of the patients receiving the drug.

JAUNDICE. Our low incidence of jaundice (1.9 per cent) is about the same as that reported in the literature. Cohen[2] reports an incidence of 1 per cent, and Delay and Deniker[14] encountered but 2 cases in a series of 1000 patients. It seems probable that the incidence of 3 per cent reported by both Goldman[8] and Lehmann[5] is too high. The incidence of jaundice appears to vary according to the dosage. Doughty[15] compiled the available data on the subject and reports an incidence of 1.4 per cent in patients receiving high doses (200 to 2400 mg./day). In lower dose ranges he found an incidence of 0.8 per cent. In this respect our experience with jaundice is at variance with those investigators who definitely associate the development of icterus with high doses of chlorpromazine. In our study no jaundice was reported in patients who received a dosage higher than 400 mg./day.

BLOOD CHANGES. Our findings on the occurrence of agranulocytic angina support the contention by various writers that true cases of malignant agranulocytosis associated with chlorpromazine therapy are extremely rare. Boleman[16] reports a single fatal case; Goldman,[8] 3 nonfatal cases; and Lomas,[17] 1 nonfatal case. In our study we found no cases of the disease. The low incidence of blood changes detected in patients allowed us to modify our program of blood studies undertaken to safeguard the patients in our series. At the onset of the evaluation of chlorpromazine, the accepted procedure was to make a blood study of each patient every two weeks. Because of the low incidence of blood changes, our procedure was modified to one study every four weeks.

LOBOTOMY. Various staff members have independently observed that some of the effects of chlorpromazine were not unlike those witnessed following lobotomy. One physician expressed the impression that chlorpromazine seemed to produce a "chemical lobotomy." (This statement was made prior to and independent of a similar observation by Pollack.[18]) It is probably due to this effect of chlorpromazine that not a single lobotomy has been performed at the Topeka State Hospital since the introduction of the drug.

SECLUSION AND RESTRAINT. One of the most valuable effects of chlorpromazine therapy has been the decreased need for seclusion and restraint. The resulting fall in tension on the wards has been highly beneficial to both patients and personnel. Chlorpromazine's most dramatic benefit was seen on wards where before the drug was given a particularly aggressive and dangerous patient had completely hamstrung the efforts of ward personnel to conduct and maintain a therapeutic program. On one such ward where there had been a number of very aggressive patients, chlorpromazine helped the patients so much that the ward was

able to hold an open house for the first time. Patients who once had been unmanageable acted as guides and proudly displayed the improvements that had been made on their ward. One visitor who had been ward physician to this group of patients before chlorpromazine had been introduced into the hospital was so impressed by the changes—both in ward atmosphere and in the patients themselves—that he wrote to me commenting on the excellent, "almost unbelievable" improvements.

It is interesting that there has been a growing dependency on the drug by all personnel, and by nursing personnel in particular. This dependency far exceeds that formerly given to electroconvulsive therapy for the management of the acutely disturbed patient. Many physicians have also observed this phenomenon. Lehmann,[5] for example, noted, "The nursing personnel soon learn to appreciate its favorable effects and the introduction of the drug has indeed changed the whole aspect of the acute treatment and observation wards through reduction of noise and confusion . . ."

SUMMARY

For the past year, 37 physicians at the Topeka State Hospital have evaluated the effects of chlorpromazine in 321 patients under treatment for various neuropsychiatric ills. Effectiveness of drug therapy was arrived at by an evaluation of 24 items covering various aspects of symptomatology. The consensus of the rating of these items was then utilized to arrive at an over-all evaluation of response to the drug. This report summarizes their findings on the drug's optimal dosages, efficacy, specificity, effect upon symptoms, incidence of untoward reactions, and the effect on concomitant therapies.

Dosage. A dosage of 200 to 250 mg./day of chlorpromazine was found effective for most patients. Few patients who failed to respond to this quantity of the drug showed any benefits from larger amounts. However, the optimal dosage must be "individualized" for each patient.

Efficacy. Chlorpromazine is not uniformly effective in the hands of all therapists. The drug's efficacy varied considerably depending on the physician's attitude; physicians who favored chemotherapy found chlorpromazine much more valuable than did those who rejected the concept. The over-all "success rate" showed that 65.5 per cent of the patients were moderately to markedly improved, and only 6.4 per cent of the patients showed no benefit from therapy. Of all patients treated, 26.5 per cent have either been separated from the hospital or are in the process of separation after one year of treatment, despite the fact that their average length of illness was over 10 years.

A study of 14 patients who received a combination of chlorpromazine and reserpine seems to indicate that the combination is more effective than either agent alone.

Specificity. The efficacy of chlorpromazine therapy varied according to the type of illness treated. Fifty-two per cent of all patients with schizophrenic reactions showed moderate to marked improvement—patients with schizoaffective, paranoid, or catatonic reactions were most benefited by the therapy. Among manic-depressive patients, 78 per cent of those in the manic phase were moderately to markedly improved; 89 per cent of the patients with involutional psychotic reactions were also moderately to markedly improved.

Forty-three per cent of patients with organic brain syndromes showed similar improvement —those with cerebral arteriosclerosis responding best.

Effect on Symptoms. The most conspicuous effect of chlorpromazine therapy is the lessening of hyperactivity and tension. Those behavior traits that stemmed from these symptoms were most affected. However, the drug was of some help in improving almost all symptoms of mental illness.

Untoward Reactions. The most common side effect was drowsiness, which was seen in 22.8 per cent of the patients treated. Other reactions, such as parkinsonism, skin rash, dizziness, etc., were each found in less than 4 per cent of all patients. The incidence of jaundice was only 1.9 per cent, blood changes 1.9 per cent, and hypotension 2.8 per cent. Almost without exception, the untoward reactions were mild and neither auxiliary medication nor withdrawal of chlorpromazine was required to produce remission of the side effect.

Concomitant Therapies. There appears to be some reduction in the number of electroconvulsive therapy or insulin coma treatments given throughout the hospital since the introduction of chlorpromazine. However, the effect of chlorpromazine on our lobotomy program has been profound. Not one lobotomy has been performed since the drug was introduced although the surgical procedure was a regular part of our program previously. The effect of chlorpromazine on patients has been likened to a "chemical lobotomy" by various members of the staff.

CONCLUSION

During the year of this study there has been a gradually increasing acceptance of chlorpromazine to the point where it now enjoys the same status as electroconvulsive therapy and insulin coma therapy. It has been found superior to older forms of therapy in the treatment and management of the chronically psychotic patients and has become the treatment of choice for acute psychomotor excitements. Chlorpromazine's greatest value may lie in its ability to prepare patients for, and make them more amenable to, various psychotherapeutic procedures. If used on a sufficiently large scale, it may radically alter our present measures for the management of the acutely disturbed and chronically psychotic patient.

RESUMEN

Durante el año de estudios hechos con Thorazine, se ha visto que su aceptación ha ido en aumento gradual, hasta el punto de que en la actualidad disfruta del mismo rango que la terapia por electrochoque y el coma por insulina. Se halló superior a los viejos sistemas terapéuticos empleados en pacientes psicóticos crónicos y se ha convertido en el tratamiento de elección para las excitaciones psicomotoras agudas. El mayor valor de la Thorazina radica en sus posibilidades para preparar a los pacientes y hacerlos más adaptables a los diferentes procedimientos psicoterápicos. Si se usa en una escala suficientemente grande, puede alterar en forma radical nuestras medidas actuales para el tratamiento de pacientes con trastornos psicóticos agudos y crónicos.

RESUME

Pendant l'année de cette étude, l'acceptation de la Thorazine s'est accrue graduellement de sorte que maintenant cette drogue se place au même rang que l'électrochoque et la thérapeutique insuline. La Thorazine a été trouvée supérieure aux formes plus anciennes de thérapeutique, dans le traitement et la cure des malades souffrant d'une psychose chronique, et elle est devenue le traitement de choix pour les excitations psychomotrices aiguës. La plus grande valeur de la Thorazine réside probablement dans son pouvoir de préparer les malades ou de les rendre plus soumis aux divers procédés psychothérapeutiques. Employée à une échelle assez grande, la drogue peut changer radicalement les mesures actuelles pour la cure des malades très troublés ou ceux atteints de psychoses chroniques.

BIBLIOGRAPHY

1. Feldman, P. E.: The personal element in psychiatric research, Am. J. Psychiat., June, 1956. To be published.
2. Cohen, I. M.: Effects of chlorpromazine in psychiatric disorders, Am. J. M. Sc., April, 1955.
3. Lehmann, H. E., and Hanrahan, G. E.: Chlorpromazine—new inhibiting agent for psychomotor excitement and manic states, Arch. Neurol. & Psychiat. 71:227, Feb., 1954.
4. Feldman, P. E.; Lacy, B. S.; Walker, A. E., and Garrez, N. J.: A controlled blind study of the effects of Thorazine on psychotic behavior, Bull. Menninger Clin. 20, Jan., 1956.
5. Lehmann, H. E.: Therapeutic results with chlorpromazine in psychiatric conditions, Canad. M. A. J. 72, Jan. 15, 1955.
6. Moyer, J. H.; Kinross-Wright, V., and Finney, M. R.: Chlorpromazine as a therapeutic agent in clinical medicine, Arch. Int. Med. 95:202, Feb., 1955.
7. Winkelman, N. W., Jr.: Chlorpromazine in the treatment of neuropsychiatric disorders, J. A. M. A. 155:18, May, 1954.
8. Goldman, D.: Treatment of psychotic states with chlorpromazine, J. A. M. A. 157:1274–1278, Apr. 9 1955.
9. Lemere, F.: Combined chlorpromazine-reserpine therapy of psychiatric disorders, Arch. Neurol. & Psychiat., July, 1955.
10. Tuteur, W.: Combined reserpine-chlorpromazine therapy in highly disturbed psychotics, Am. J. Psychiat. 112, Sept., 1955.
11. Elkes, J., and Elkes, C.: Effect of chlorpromazine on the behavior of chronically overactive psychotic patients, Brit. M. J., Sept. 4, 1954.
12. Azima, H., and Ogle, W.: Effects of largactil in mental syndromes, Canad. M. A. J. 71, Aug., 1954.
13. Sainz, A. A.: Clinical applications of chlorpromazine in psychiatry, Presented at the A. A. A. S. Symposium, Dec. 21, 1954.
14. Delay, J., and Deniker, P.: Neuroleptic effects of chlorpromazine in therapeutics of neuropsychiatry, J. Clin. & Exper. Psychopath. 16:104–112, April-June, 1955.
15. Doughty, R.: Science Information Department, Smith, Kline & French Laboratories, Aug., 1955.
16. Boleman, A. P., Jr.: Agranulocytosis associated with administration of Thorazine, J. A. M. A. 157, Jan. 22, 1955.
17. Lomas, J.: Chlorpromazine and agranulocytosis, Brit. M. J., Aug. 7 1954.
18. Pollack, B.: Mental illness, M. Times, May, 1955.

Epinephrine Derivatives as Potential Schizophrenic Factors

*A. Hoffer, M.D., Ph.D.**
Saskatoon, Saskatchewan, Canada

In the 50 years since the synthesis and characterization of epinephrine, much has been learned of its pharmacology and biochemistry. For many years it was considered the chemical mediator of the sympathetic nervous system (sympathin), comparable in function to acetylcholine. The isolation of norepinephrine, the precursor of epinephrine, and the study of its properties have clearly shown that it is the sympathetic mediator released at the synaptic terminals. Undoubtedly epinephrine must play another important role in the physiology of the animal. Goodman and Gilman[51] state: "The sympathoadrenal system is not essential to life and animals completely deprived of it can continue a fairly normal existence within the sheltered confines of the laboratory. . . . Under circumstances of stress however the lack of sympathetic adrenal functions become evident. In cats for example, body temperature can not be regulated when the environment is hot or cold; the blood sugar level does not rise in response to urgent need; compensatory vascular responses to hemorrhage, oxygen want, excitement and work are lacking; resistance to fatigue is lessened; sympathetic components of instinctive reactions to fright and danger are lost; and other serious deficiencies in the protective forces of the body are discernible." As Hoskins[65] has shown, these autonomic changes are reminiscent of the ones present in schizophrenia. It is therefore important to examine closely the relationship between the autonomic nervous system, and specifically the role of epinephrine and its metabolites, and schizophrenia.

Cannon[24] outlined the hypothesis that epinephrine is the emergency mediator of the body. It prepares the animal for action, either defensive or offensive, in the following ways: (1) by causing a redistribution of blood toward muscle, heart, and brain; (2) by producing hyperglycemia and insuring an adequate supply of energy for brain and muscle; (3) by increasing bronchiolar dilatation and promoting increased efficiency of gaseous exchange; (4) by shortening coagulation time; (5) by acting as a metabolic stimulant of carbohydrate metabolism; (6) by relaxing detrusor muscles and constricting the sphincters; (7) by producing a lysis of eosinophils and lymphocytes; and (8) by increasing secretion of thyrotropic hormone of the anterior lobe of the pituitary gland.[17] Stimulation of the sympathetic nervous fibers of the adrenal gland increases the methylation of norepinephrine to epinephrine.[17] Epinephrine, when injected intrathecally, [80, 81] produces surgical anesthesia, with no effect on blood pressure or electroencephalographic or electrocardiographic findings. Fortunately, it does not readily penetrate the blood brain barrier, where it would markedly interfere with cerebral glucose metabolism.[56]

Supported by National Health Grants, Ottawa, Ontario, and the Rockefeller Foundation, New York, N.Y.

* Director of Psychiatric Research, Department of Public Health, University Hospital, Saskatoon, Saskatchewan, Canada, and of Saskatchewan Committee on Schizophrenia Research.

Epinephrine fulfills admirably its postulated role as an emergency mediator. The acceptance of this concept removes the need for argument as to its role as a specific or nonspecific stress.[113, 45] Obviously, any factor that increases epinephrine output will bring about the physiologic accompaniments of stress. The ability to react normally to stress will depend upon the presence of sufficient circulating epinephrine for the duration of the stressful event. There must be rapid synthesis, i.e., a rapid rate of methylation of norepinephrine and a low rate of inactivation. Defective reactivity to stress may result from defective synthesis or overactive destruction. Severe stress, i.e., injection of large quantities of insulin in cats, produces a decrease in epinephrine due to inability of the methylation system to keep pace with the demand.[21]

The schizophrenias have proved so baffling in their variety and scope that as yet no rational hypothesis has been developed to satisfactorily synthesize the wealth of published data regarding them. The etiology is unknown, but the etiologies hypothesized are numerous. They vary from purely psychologic to purely organic. The confusion associated with this syndrome is by no means due to lack of investigation, interest, or speculation. The literature at the present time is so vast that it is practically impossible to search it adequately. So much of the data appears contradictory that it seems a hopeless task to reconcile the host of accurate observations into a consistent hypothesis of schizophrenia.

Woolley[140] has recently written: "The sequence of events in the emergence of each new idea has usually been first the chance discovery of isolated and unexpected facts. This is then followed by the recognition of the underlying principle. Such recognition frequently results from the bringing together in the mind of one individual a group of heterogenous and isolated cases. Each member of this group is seen to be an example of an underlying new phenomenon. The two states of discovery are both essential. So long as unpremeditated and unexplained findings are recorded and left to be forgotten they do not constitute discovery. Only when they are activated by an inspiration of the new phenomenon do they become usable and effective knowledge. Finally, as a result of the discovery, a number of explorations are made and from these the validity of the original principle is established. In addition from these explorations, the general features of the phenomenon are recognized and classified. Occasionally these explorations lead to new discoveries which then follow a course similar to that just outlined."

Sufficient information has by now been amassed for the development of a hypothesis regarding the etiology of schizophrenia. The Saskatchewan group has developed and followed such a working hypothesis and has found it most useful in guiding the research program. Since the hypothesis relates to the autonomic nervous system, and specifically to epinephrine, and norepinephrine, a brief review will be given of the chemistry and physiology of epinephrine, norepinephrine, and two epinephrine derivatives (adrenochrome and adrenolutin). Finally the working hypothesis will be outlined and discussed in relationship to schizophrenia.

EPINEPHRINE

Synthesis. According to Martin,[93] the starting material for the in vivo synthesis of epineph-

rine is the essential amino acid phenylalanine. In its conversion to epinephrine, four changes are made, which probably occur in the following order: (1) the addition of two hydroxyl groups to the benzene ring to form β-(3, 4-dihydroxyphenyl)′-L-alanine, catalyzed by dopa decarboxylase; (2) the replacement of the carboxyl group by a hydrogen atom to form hydroxytyramine; (3) the addition of a hydroxyl to the side chain to form norepinephrine; or the decarboxylation of dihydroxyphenyl serine[10]; and (4) the methylation of the terminal nitrogen to form epinephrine. The methyl group for the conversion of epinephrine is obtained from methionine. Labeled carbon on methionine appears in the epinephrine molecule.[72] The addition of excess methionine does not increase the proportion of epinephrine,[68] although animals maintained on methionine-deficient diets contain a smaller proportion of epinephrine in the adrenal medulla.

Dopa decarboxylase catalyzes the loss of the carboxyl group from tyrosine. This is present in the adrenals. It is active only when there are two hydroxyl groups on the benzene ring and when the terminal nitrogen is free of methyl groups. Tyrosine and phenylalanine block the action of dopa decarboxylase by substrate displacement. There are no known natural inhibitors. Folic acid antagonists inhibit dopa decarboxylase and produce a marked drop in blood pressure in animals.[94, 95]

Destruction. The pathways for epinephrine detoxification are not clearly known, but several are suggested.[3] Epinephrine, which is liberated in small quantities, is distributed to all the tissues of the body by arterial blood and is not inactivated by the liver to a greater extent than it is by muscle. It may be excreted in the urine unchanged or may be modified by several enzyme systems. These changes may occur at the methyl group, at the hydroxyl groups of the benzene ring, or at the secondary alcohol and the amino group.

EXCRETION OF EPINEPHRINE: This does not occur when it is administered in physiologic quantities. When given in large dosages to dogs, small amounts are found free in the urine.

STORAGE OF ACTIVE EPINEPHRINE: Epinephrine rapidly leaves the body fluids and enters the tissue cells. In vitro it enters the erythrocytes and may remain active there up to 10 hours. It is recovered by the laking of the red blood cells.[4] There are no destructive enzymes in normal serum. On the contrary, the reducing property of blood due to ascorbic acid, glutathione, and amino acids protects epinephrine from auto-oxidation. The adrenal medulla may store epinephrine, as do other tissues, apparently in the granules of the cells.[12] When epinephrine is injected, the concentration in the tissues rises. In vivo, free epinephrine very rapidly disappears from the serum but may appear in the urine for a long time after the injection, i.e., some of the stored epinephrine is slowly released and detoxified. Recently Heath[55] and co-workers showed that, when epinephrine was added to the serum of normal persons, it was relatively stable but that, when it was added to the serum of schizophrenics, it was rapidly converted into a fluorescent substance having some similarity to adrenochrome.

DEMETHYLATION: Norepinephrine is methylated to form epinephrine, but the reverse does not occur in the body.

CHANGES OF SECONDARY ALCOHOL: Oxidation of this group will occur but in conjunction with the oxidation of epinephrine to adrenochrome and beyond.

DEAMINATION OF SIDE CHAIN: Amine oxidase deaminates tyramine, aliphatic monoamines, and secondary amines of the epinephrine type by converting the amine into an aldehyde. It is present chiefly in the liver, the intestinal tract, and the central nervous system and provides one of the mechanisms for the inactivation of epinephrine in the body. The epinephrine is converted into 3,4 dihydroxyphenyl hydroxyacetaldehyde. The aldehydes are rapidly destroyed in vivo and have no known physiologic properties. Teague and Wingard[122] indicate that the aldehydes may have sympathomimetic properties. Amine oxidase is not specific for epinephrine, as it deaminates all amines with the carbon chain "-C-CH_2-N." Burns[20] has shown that norepinephrine is preferentially deaminated when both norepinephrine and epinephrine are present.

Burns[20] believes that amine oxidase plays a role in the sympathetic nervous system comparable to that of acetylcholine esterase in the parasympathetic system. The enzyme has been found around the sympathetic nerve endings in blood vessels, in the nictitating membrane, and in the iris of the cat. It destroys norepinephrine more readily than epinephrine and thus decreases the quantity of circulating norepinephrine. In denervated vessels amine oxidase levels fall, and the sensitivity to norepinephrine increases. Thyroid feeding decreases the amine oxidase levels of liver. This probably accounts for the increased pressor and hyperglycemic response after epinephrine injection. Thyroidectomy increases amine oxidase levels.

Ephedrine and amphetamine, not deaminated by amine oxidase, are excreted unchanged and potentiate the activity of epinephrine. They increase the amount of epinephrine liberated by sympathetic stimulation of rabbits' ears.

Blaschko[7] found that inhibitors of amine oxidase contained the following structure: "R-C-CH_2-NH-CH_3." Beyer[6] reported that phenylpropylamines having the amino group on the terminal carbon were oxidized by amine oxidase but that, if hydroxyl groups were attached to the ring, the compound was oxidized by phenolase. If the benzene ring contained no hydroxyl, and if the amino group were on carbon adjacent to the terminal carbon, neither enzyme could oxidize epinephrine. The following compounds, among others, are inhibitors of amine oxidase: cocaine, ephedrine, indole, indoleacetic acid, cadaverine, histamine, phenylisopropylamines, desoxyephedrine, *d*-desoxyephedrine hydrochloride, adrenochrome, urea, caffeine and other purines, amphetamine, and nicotine.

Bacq,[3] in his review, maintains that amine oxidase inactivation does not provide an adequate explanation for the rapid disappearance of low concentrations of epinephrine from the blood and gives seven arguments to support this view. 1. Amine oxidase is present chiefly in the liver, intestine, and central nervous system, where it probably protects against toxic amines absorbed from the intestine. 2. Amine oxidase is absent in other tissues that inactivate epinephrine as quickly. 3. The rate of inactivation by amine oxidase is very low. 4. The functional removal of the liver or intestine does not sensitize the animal toward epinephrine. 5. Other tissues inactivate epinephrine at the same rate as does the liver. 6. Ephedrine and cocaine need not act through inactivation of amine oxidase. They have a direct action on receptor cells. 7. Other efficient inhibitors of amine oxidase do not sensitize toward epinephrine.

ESTERIFICATION OF PHENOLIC HYDROXYLS: As both phenolic hydroxyls are essential for pressor activity, oxidation or esterification results in complete inactivation. It has been shown that epinephrine may be detoxified by sulfoconjugation at either of the phenolic hydroxyls.[3, 108, 124] Substantial quantities of sulfoconjugates are recovered in the urine after oral or parenteral administration of large quantities. Esterification by sulfoesterase may be the major detoxicative mechanism in the body. Sympathomimetic amines not deaminated by amine oxidase are esterified to a greater degree than are the amines oxidized by the oxidase. Further, cocaine interferes with esterification by esterase and thus may potentiate epinephrine activity. Phenols may also potentiate by this mechanism.

OXIDATION TO QUINONES: In vitro, epinephrine auto-oxidizes to form a reddish-colored solution containing adrenochrome and other metabolites or degradation products. This process is accelerated by the heavy metals, by alkaline *p*H, and by light and is inhibited by strong reducing agents such as ascorbic acid, cysteine, 2,3-dimercapto-1-propanol (BAL), and thyroxine. According to Bacq,[3] the oxidation of epinephrine to adrenochrome plays an important role in the metabolism of epinephrine. The properties of adrenochrome and a discussion of its possible occurrence in the body will be discussed further on.

OTHER MECHANISMS: The phenyl ring probably can be broken just as can that of tyramine.

In summary, there are at least three important mechanisms involved in the detoxification of epinephrine: (1) deamination by amine oxidase with the formation of metabolizable aldehydes; (2) esterification with sulfate to form excretable sulfate esters; and (3) oxidation by phenolases to adrenochrome or similar substances with properties not yet clearly defined.

Secretion. Epinephrine is present in the blood at a concentration of about 3 to 5 μg./liter. Under stress, it is secreted in increased quantities. Swan,[119] as a result of intravenous infusion studies with epinephrine, concluded that during stress the secretion rate was about 10 μg./minute (0.6 mg./hour, or 14.4 mg./day). Guyton and Gillespie,[53] using constant intravenous infusion in dogs under complete spinal anesthesia, found that the normal rate of secretion was 0.45 μg./Kg./minute. This value is approximately twice that recorded by Stewart and Rogoff[118] for the adrenal medulla production. These authors concluded that "approximately half of the blood pressure sustaining activity under normal conditions is due to adrenal secretion of adrenaline and the other half to the sympathetic activity elsewhere." This contradicts the view that under resting conditions the adrenal medullary secretion has no function and explains why removal of both adrenal medullae does not result in marked hypotension.

Although it is known that, in general, stress results in increased secretion of epinephrine, very few studies have outlined in detail the effect of various factors, such as the following, on the rate of secretion.

ANOXIA: Caused by deficient oxygenation of perfused adrenal glands or by potassium cyanide, anoxia increased the epinephrine output but caused a total loss of epinephrine from the circulating system.[17]

SYMPATHETIC STIMULATION: The effects of splanchnic stimulation depend upon the initial concentration of epinephrine in the perfusion fluid. When there is a low concentration in the perfusion fluid, there is little epinephrine discharge. As the concentration in the fluid

is increased, the discharge from the gland increases toward a maximum. Beyond that point, increasing concentration in the perfusion fluid results in a decreased discharge.[17] Splanchnic stimulation increased the proportion of epinephrine to norepinephrine.[21]

INSULIN HYPOGLYCEMIA: It appeared clearly established, using bioassay, that during insulin coma there was an increased discharge of epinephrine from the adrenal medulla. Weil-Malherbe and Bone[130], using their fluorometric assay method, reported that there was a decrease in the epinephrine level in venous blood. The lowest level is reached one-half hour after the injection, and it then gradually returns to normal one hour after termination of the coma. Recently, Weil-Malherbe and Bone[130] suggested that differences between bioassay and fluorometric assay are due to differences in collection methods. About 70 to 80 per cent of amine content of plasma are in platelets.

Electroshock Therapy. Sympathetic phenomena are observed with electrical stimulation, i.e., an elevation of blood pressure, an increased blood sugar level, etc. Weil-Malherbe[131] has shown that the passage of the electric current through the brain is such a powerful stimulant of epinephrine production that, during hypoglycemic coma when the medulla is already functioning at about 10 times its normal level, the current leads to a pronounced increase in blood epinephrine levels and occasionally lifts the coma.

Parasympathetic Stimulation. Since acetylcholine directly controls the level of activity of the adrenal medulla, any factor increasing the acetylcholine level of arterial blood should increase the secretion of epinephrine. This may be accomplished by a natural increase in the acetylcholine level or by blocking acetylcholine esterase. It is probable that stress will release acetylcholine, which then pushes the adrenal medulla. The esterase inhibitors such as neostigmine and eserine have been shown to increase the epinephrine levels of blood. Atropine blocks the muscarinic activity of acetylcholine and also of esterase. It should therefore increase the secretion of epinephrine. Danielopolu[27] reported that after use of atropine, acetylcholine caused vasoconstriction and stimulated the medulla to liberate epinephrine. This effect was abolished by adrenalectomy.

The author[58] found that 3 mg. of atropine produced an elevation of systolic blood pressure and changes in leucocyte counts characteristic of epinephrine.

Glutamic Acid and Related Compounds. Weil-Malherbe and Bone[130] have shown that glutamic acid, l-arginine, glycine, and succinate induce a significant rise in the blood epinephrine level. Glutamate and arginine have the most pronounced effect. The arousal of the subject from insulin coma by the use of glutamate appears to be due to the drug's adrenergic properties.

Effect of Hallucinogens. Both lysergic acid diethylamide (LSD) and *d*-desoxyephedrine hydrochloride produce an elevation of epinephrine levels followed shortly after by a decrease. Finally, the blood levels are above the resting level for several hours.

Psychologic Properties of Epinephrine. Surprisingly little has been published regarding the central nervous system activity or, more correctly, the psychologic activity of the sympathomimetic compounds. This is in striking contrast to the numerous studies on the physiologic relationships; possibly, this is due to the pressor activity of epinephrine, which prevents its use in psychologic studies in dosages of more than 1 mg. The sympathomimetic

compounds, in addition to their pressor activity, include many of the better known euphoriants and hallucinogenic compounds or are closely related to them.

Landis and Hunt[75] reviewed the literature, relating epinephrine to emotional reactions. They found that injections of epinephrine, contrary to the then current opinion, could produce genuine emotional change. They tested a group of mentally ill people by injecting up to 1.5 mg. of epinephrine intramuscularly and observed the emotional changes. They concluded that it could reproduce the physiologic picture associated with anxiety. The various groups of mental disorders, varying from manic-depressive to schizophrenic states, showed no difference in susceptibility. Whether the subjective experience with the use of epinephrine was genuine emotion, or an "as if" phenomenon, depended upon the willingness of the individual to equate his feelings with previous experience. Landis[74] and Cantril and Hunt[26] found that most of their subjects demanded a satisfactory reason for emotion before the experience could be felt as complete.

Lindemann[86] reported a psychopathologic study of epinephrine in various diagnostic groups. The total setting of the individual was studied, and the reactions to 1 mg. of epinephrine was assessed. Four patients in a manic excited phase became less excited and appeared clinically improved. Eight neurotics felt a marked increase in tension. Seven schizophrenics became more excited, 4 (2 of them showed deterioration) showed no change in behavior, and 2 depressive patients became suicidal. Of special interest was the observation that in 1 individual epinephrine decreased manic excitement but that later when he had improved clinically it markedly increased his tension. The chief effect of epinephrine was in increasing anxiety, self-concern, and tension and in exaggerating instinctual needs, with aggravation of conflict. The emergency situation was an imbalance produced by the increased drive, with no corresponding increase in the possibility for direct expression of the drive.

The development of anxiety after the administration of epinephrine is well established, although the mechanism of this action is not clear.[2] Agents that block the reflex liberation of epinephrine inhibit or prevent anxiety. The anxiety is not the result of hypertension. Altschule implicates epinephrine degradation products in the production of anxiety, since they resemble methoxy derivatives of phenylethylamines in structure. These substances, including mescaline, produce anxiety. As will be shown later, there is no need to postulate that anxiety is related to the epinephrine degradation substances. It may be due entirely to the effect of unchanged epinephrine. Adrenochrome and adrenolutin[61, 63] decrease subjective awareness of anxiety.

Few studies have been made of the effect of epinephrine upon intellectual function, especially on abstract and concrete reasoning. Since epinephrine is commonly used in medicine, one might expect that, if it did produce changes, they would have been reported. Epinephrine is used in medicine for emergency situations, when the physician is not interested in the intellectual performance of his patient, and for the relief of asthma and some of the allergies. Patients who use epinephrine regularly provide fertile ground for investigation of its effect upon thought processes. Hoffer, Osmond, and Smythies[63] reported several instances in which administration of epinephrine produced visual hallucinations similar to

those produced by mescaline. By interviewing 5 asthmatic patients who habitually used large quantities of epinephrine, the author discovered 2 normal (apart from their asthma) individuals who invariably felt some difficulty in thinking when epinephrine was administered to them, at the same time feeling the relief of their asthmatic condition. One subject upon questioning reported thought blocking similar to that found in some schizophrenic patients. The author has known 1 person with angioneurotic edema who required epinephrine as a life-saving measure. Shortly after the administration of epinephrine, she suffered a schizophrenic psychosis of short duration. These few instances, of course, are not convincing to the critical observer, but they do provide evidence that here there is a fertile area for further inquiry. Is it possible that many of the reported conversions of asthma to schizophrenia have been facilitated by the use of large quantities of epinephrine as a treatment of the asthmatic condition?

The relationship of epinephrine to schizophrenia has, until recently, required the presence of anxiety as the intermediary. That the relationship might be more direct was suspected by de Jong,[28] who noted the chemical similarity between mescaline and epinephrine and their ability to produce catatonia in animals. Mescaline, which induces psychologic changes in human beings similar to those found in some schizophrenics, has raised hopes that a similar substance might be found in the body. The presence of substances more closely related to mescaline was first investigated, but no one was able to find any methoxy substances in the urine, except after the administration of mescaline. Recently, however, Boscott[13] found methoxy compounds in the urine of phenylpyruvic acid oligophrenics by using more accurate chromatographic techniques.

The essential importance of the similarity between mescaline and epinephrine was not grasped for some time until Osmond and Smythies[100] independently made the same observation and re-emphasized the importance of this observation. They suggested that schizophrenics may contain within them an "M" substance, intermediate in structure and function between epinephrine and mescaline. This observation eventually led toward the study of adrenochrome, as described by Osmond.[99]

Of course, the suggestion that toxins are causally related to schizophrenia is not new (about 60 years of age)—relatively a young hypothesis compared to its antagonistic hypothesis that schizophrenia is an illness induced upon the person by factors from without his physiologic structure. The latter theory probably antedates the dawn of history. Toxic amines and toxic basic substances have been diligently searched for.[23] However, it is impossible to isolate any substance unless some of its attributes are known and can be used for its assay. The isolation of a possible toxin whose only known property is to induce schizophrenia appears quite hopeless, since animal experimentation is so inadequate. In order to give direction to the search, the literature was examined for substances that reportedly have produced in human beings psychologic changes of a psychotic nature in the presence of normal consciousness, memory, and orientation (in the dosages normally used). This narrowed the field considerably and eliminated from consideration narcotic substances and other chemicals that produce, by psychiatric definition, toxic psychosis, i.e., changes in the presence of decreased levels of consciousness, defective memory, and disorientation.

Such a group of substances was discovered[63] and was found either to contain the indole nucleus or possibly to be able to form an indole nucleus, with one exception. Since then, two other substances have been found—bufotenin[38] and adrenolutin,[61] both indoles. It therefore seemed reasonable to start the search for the schizophrenic toxin by looking for indoles in the body. The relationship of schizophrenia to the autonomic nervous system, especially the sympathetic branch, necessitated consideration of a substance related to sympathetic function. Indoles are formed endogenously from tryptophan and tyrosine metabolism through the formation of epinephrine. The tryptophan relationship to schizophrenia appeared less probable and not as readily related to stress and the clinical autonomic manifestations of schizophrenia. The hypothesis called for an examination of adrenochrome, and, much later, adrenolutin, as a potential schizomimetic substance.

Shortly after Hoffer, Osmond, and Smythies[63] reported that adrenochrome was hallucinogenic, inhibited cerebral in vitro respiration, and produced electroencephalographic abnormalities in epileptics, Rinkel, Hyde, and Solomon[110] re-emphasized that the epinephrine cycle was somehow disturbed in schizophrenia and suggested that LSD produced its psychotomimetic effect by interfering with enzymes of the epinephrine cycle. This is a useful hypothesis and is reinforced by Liddell and Weil-Malherbe's[85] observation of the phasic changes in concentration of epinephrine in blood induced by LSD and *d*-desoxyephedrine hydrochloride. When epinephrine is injected intracisternally, it produces analgesia, sleep, and anesthesia. Leimdorfer and Metzner[81] found sleep, analgesia, and anesthesia in dogs given 0.5 to 1.0 mg./Kg. of epinephrine. Norepinephrine had a similar but less pronounced effect. In 1 of 2 human patients in whom 2 mg. of epinephrine were injected, deep sleep occurred.[80,82] Feldberg and Sherwood[42] found that epinephrine produced licking movements and swallowing in cats during the first few minutes, followed by vomiting and swallowing. Within 10 to 20 minutes, a state of light anesthesia developed. The effect wore off within an hour, with full recovery in three hours. These authors raised the question whether "a large output of adrenaline and nor adrenaline in the circulation can produce central effects like those seen in cats on intraventricular injection, and whether the state of 'exhaustion' or 'fatigue' which follows strong emotional discharge of Cannon's so-called emergency states can be reactions accounted for in this way."

Marrazzi[92] has shown that epinephrine in microgram quantities produces inhibition of synaptic transmission in the central nervous system, as do serotonin, bufotenin, and, in much larger quantities, adrenochrome.

Effect of Differential Inhibition of Enzyme Systems That Detoxify Epinephrine. There are several pathways for the metabolism of epinephrine in the body. Two of these are considered biologically important, i.e., via amine oxidase and sulfoesterase. A third system is theoretically possible by means of some phenolase, with the production of a quinone indole. Substances that will differentially inhibit these systems may drive epinephrine into unusual metabolic pathways, since the rate of destruction must equal the rate of synthesis and release. Blocking the phenolase enzyme systems will force epinephrine through the amine oxidase and sulfoesterase system. Martin et al[96] found that *p*-aminobenzoic acid inhibited the action of tyrosinase on epinephrine. This vitamin produced mild hyperglycemia in

dogs and increased blood pressure in anesthetized cats.[93] This provides some evidence that, in vivo, phenolase systems can act on epinephrine. Perhaps the vitamin in large quantities would be useful in the treatment of conditions characterized by an overproduction of adrenochrome or adrenolutin.

Substances that block amine oxidase and/or sulfoesterase may drive epinephrine through a phenolase-inactivating system while potentiating the action of epinephrine. Blaschko[7] first associated inhibition of amine oxidase with a unique chemical structure, the ethene amine nucleus. A very large series of compounds possess the nucleus and block amine oxidase. This series includes an interesting group of euphoriants, narcotics, and autonomic drugs, e.g., cocaine (euphoriant and hallucinogen), ephedrine, amphetamine, *d*-desoxyephedrine hydrochloride, (central nervous system activators, euphoriants, and, in large quantities, hallucinogens), and LSD, which produces similar changes in blood epinephrine.[85] This suggests that LSD is active in a similar way and may inhibit amine oxidase. Marsilid (1-Isonicotinyl-2-isopropylhydrazine) is a very active amine oxidase inhibitor.[141] When used for the treatment of tuberculosis, it has produced stimulation and a sense of well-being in schizophrenic patients. Kamman et al[71] noted little change in mental states. Isoniazid, a much weaker amine oxidase inhibitor, is not a euphoriant and has no effect on the mental state of mentally ill tuberculous patients.[66] Both compounds have induced schizophrenic-like psychoses, but Marsilid causes many more mental symptoms than isoniazid.[135, 104]

Blocking sulfoesterase will increase the load on other enzymes. Torda[124] found that cocaine blocked esterification by sulfoesterase. Richter[108] believed that phenols potentiated epinephrine because of a similar action.

Blocking either sulfoesterase or amine oxidase will increase the load on the nonblocked systems. Some substances may block both sulfoesterase and amine oxidase and show much greater psychologic activity. Cocaine blocks both. Perhaps this accounts for the well-known psychologic activity of cocaine.

Substrates of amine oxidase, if present in large concentration, may interfere with other substrates by competitive action. N-methyl tryptamine, 5 hydroxytryptamine (serotonin), N-methyl-5-hydroxytryptamine, and bufotenin are substrates for amine oxidase.[36] Blaschko[8] and Blaschko and Philpot[11] suggest that removal of serotonin is a normal function of amine oxidase. Serotonin may thus tie up amine oxidase and force epinephrine metabolism through another pathway. When given intravenously (0.25 to 0.5 mg./log) to a vagotomized cat under dial anesthesia, serotonin reinforces and prolongs the pressor action of epinephrine.[78] According to Brodie,[16] animals fed 5-hydroxytryptophan develop a toxic picture resembling that induced by LSD. The amino acid is rapidly converted in the brain to serotonin, which is changed by amine oxidase into 5-hydroxyindole acetic acid. The latter compound is found in the urine in increased concentration. It is thus possible that, because the amine oxidase is tied up with excessive quantities of serotonin, central epinephrine is detoxified via a phenolase system, with the production of adrenochrome or adrenolutin, both active compounds when administered intraventricularly in cats.[114] This may also explain the gentle action of serotonin intraventricularly[42] as compared to epinephrine.

Rate of Destruction of Epinephrine. Guyton and Gillespie[53] reported that the rate of

epinephrine destruction in the dog's body is directly proportional to the total quantity of active epinephrine in the body at a given time. The rate was 0.63Q/minute, where Q was the quantity of active epinephrine. Since the only physiologic measure of epinephrine activity was blood pressure, this finding should have been qualified by the statement that, as far as blood pressure was concerned, there was this rate of disappearance. Bacq,[3] in his review, showed that epinephrine could be stored, deaminated, sulfoconjugated, or oxidized to indole substances, each change resulting in loss of pressor activity but only the latter three resulting in destruction. Epinephrine can be stored in cells and later released. The rate of chemical destruction therefore is still unknown as a variable dependent on epinephrine concentration. It is, however, clear that, once tissues have become saturated, and with a constant rate of epinephrine secretion, as much epinephrine must be metabolized as is secreted. Under stress, increased production need not be followed to the same extent by increased destruction. Some of the excess epinephrine may be stored and after the stress period may be slowly released and metabolized.

NOREPINEPHRINE

It is now accepted that norepinephrine is the transmitter substance of the sympathetic nerve endings.[37, 119] It acts at or near the site of liberation, and very little escapes into the general circulation. Its over-all activity results in normal peripheral vasomotor resistance. Goldenberg et al[49] found that infusion of norepinephrine caused an increase in blood pressure, an unchanged or decreased cardiac output, increased peripheral resistance, and a decreased pulse rate. Swan[119] confirmed these findings but found a slight increase in heart rate. Both groups of workers report that norepinephrine is a strong vasoconstrictor of vessels of the denervated hind limb of the cat, whereas epinephrine causes vasodilatation. Denervation increased the reaction of the nictitating membrane to norepinephrine much more than to epinephrine. The authors postulated that some mechanism was present for protecting the tissues from circulating norepinephrine, which was destroyed by denervation.

Norepinephrine is metabolized slowly in the body,[101] causing only a moderate rise in the blood sugar level,[89] and does not stimulate the secretion of ACTH.[91] It appears to have little ability to reproduce the usual emotional reactions of epinephrine. Swan[119] found that norepinephrine produced mild symptoms usually unfamiliar to the subjects, although fear was occasionally found. This, of course, is consistent with the view that norepinephrine acts at, or near, its site of liberation and that only minute amounts leak away into the general circulation. Burn[20] suggested that amine oxidase is the enzyme that destroys norepinephrine at the sympathetic nerve endings and prevents it from escaping into the general circulation.

Ratio of Norepinephrine and Epinephrine. The sympathomimetic substance of the adrenal gland is a mixture of norepinephrine and epinephrine. This was shown chemically by Goldenberg et al[48] and others. U.S.P. epinephrine was shown to contain up to 36 per cent of norepinephrine. Holtz and Schumann[64] found norepinephrine present in the normal adrenal medulla of man, and Goldenberg et al[49] showed that it predominated in the adrenal

glands in cases of pheochromocytoma, resembling the adrenal gland of the whale.[22] Even more significant is the resemblance to fetal adrenal medulla.[133] West et al[133] found that, the adrenal glands of babies contained more than 90 per cent of norepinephrine, indicating defective methylation. Toward the second year of life, more complete methylation occurred. The organs of Zuckerkandl were especially rich in norepinephrine. At the second year of life, fetal cortex has been replaced by mature cortex, and the medulla is well formed. One patient with Addison's disease showed defective methylation. This suggests that the cortex is concerned with methylation, as has been confirmed by Burn.[20] In mammals with a relatively large medulla, e.g., the rabbit and guinea pig, methylation of norepinephrine is nearly complete.

Assuming that epinephrine is the stress mediator, it can be seen that too small an adrenal cortex will, in addition to its inability to produce corticoid hormones, be unable to methylate sufficient quantities of norepinephrine, i.e., there will be inadequate ability to cope with stress. This, of course, does occur in Addison's disease and in infants. Richter[107] showed that the domesticated rat has an adrenal gland one-tenth to one-quarter the size of wild rats, due to a much smaller cortex. In addition to marked behavioral changes, the wild rat was much better able to cope with stress and the tame rat was physiologically not equipped to meet stress.

Epinephrine has a more marked physiologic function than norepinephrine. De Largy et al[29] have shown that, with equal amounts of epinephrine and norepinephrine, the effects of epinephrine predominate.

ADRENOCHROME

The biologic importance of adrenochrome was first noted by Kisch,[73] who found that the oxidation of epinephrine produced a red-colored substance, which he later termed "omega." It was a quinone that acted as the oxidation catalyst in biologic systems rather than epinephrine itself. Weinstein and Manning[132] crystallized omega. Green and Richter[52] succeeded in determining the structure of omega and called it adrenochrome.

Formation in Vitro. On standing, solutions of epinephrine auto-oxidize to form several unknown substances containing adrenochrome. Bacq[3] has emphasized that this red solution is not adrenochrome, because adrenochrome is very unstable and is rapidly transformed into many different substances. A solution of deteriorated epinephrine contains substances ranging from epinephrine to the polymer called melanin.

Green and Richter[52] prepared adrenochrome by using a highly purified catechol oxidase from mushroom, a concentrated solution of epinephrine, *p*H 5 to prevent melanin formation, and bubbling oxygen. Adrenochrome is more readily prepared by the oxidation of epinephrine with silver oxide in absolute methyl alcohol.[32]

Formation in Vivo. The presence of adrenochrome in mammalian tissues or blood has not been definitely established. This is not surprising since pharmacologists and physiologists have shown little interest in adrenochrome,[3] and as it is extremely unstable and difficult to manipulate. Auto-oxidation in vivo is quite unlikely, due to the presence of

many stabilizing substances. However, powerful enzyme systems, which in vitro effect this oxidation, are present in tissues. The cytochrome-indophenol-oxidase system is present in all cells and in vitro catalyzes the formation of adrenochrome. Green and Richter[52] showed that adrenochrome at concentrations as low as 6.10^{-7} was an efficient hydrogen carrier—concentrations within physiologic concentrations. More recently, Wajzer[128] reported that the epinephrine-adrenochrome system is present in mammalian skeletal muscle at a concentration of 1.10^{-7}.

Roskam and Derouaux in 1945 found that the hemostatic activity of epinephrine has a latent period of four minutes, is maximal after seven minutes, and lasts for several hours. In contrast, the maximum activity of adrenochrome is reached in three minutes with the same duration of activity. This suggests that the oxidized derivative of epinephrine is the active hemostatic agent.

Adrenochrome inhibits the mitotic rate of cells, probably because it interferes with the glycolytic cycle.[84] Bullough[18] found that, when mice were stressed by overcrowding, the adrenal medulla increased in size by 80 per cent, while the cortex increased only 30 per cent. The epidermal mitotic rate fell 60 per cent. Epinephrine in vitro was not antimitotic for epidermis but was antimitotic in vivo, i.e., by injection into mice. Adrenochrome was antimitotic both in vitro and in vivo. Bullough[18] suggested that during stress the increased quantity of epinephrine was converted into adrenochrome, which produced the antimitotic effect.

Evidence that adrenochrome is present in human beings is not available. The sensitive fluorometric tests for epinephrine and for norepinephrine do not measure the adrenochrome that might be present in blood. The basis of these methods is the adsorption of these amines on activated alumina, which does not hold adrenochrome when present in small concentration.[129] Indirect evidence that adrenochrome can be formed in blood of schizophrenics was obtained by Heath,[55] who reported that epinephrine added to blood of schizophrenics and to blood drawn from normal persons during sleep was converted into a fluorescent substance similar to adrenochrome. Lettre[83] found that when epinephrine was added to serum it turned pink and inhibited the growth of L strain fibroblasts (cells obtained from mouse epidermis). Fedoroff[39] found that blood from the majority of schizophrenics, when drawn in the morning before breakfast, showed marked toxic properties for L strain fibroblasts but not for HeLa cells. Blood from normal persons very rarely showed the same degree of toxicity, and blood from neurotics showed much less toxicity than schizophrenics.

Bacq[3] found that injection of epinephrine into large anesthetized dogs resulted in increased excretion of indoles equivalent to about 10 to 20 per cent of the injected epinephrine. This paralleled the excretion of the epinephrine sulfate produced by esterase. Richter's[108] finding that no indoles were in the urine after consumption of large quantities of epinephrine does not prove that adrenochrome cannot be formed. When rabbits were injected with adrenochrome, neither adrenochrome nor indoles were found in the urine.[3]

Improved techniques of analysis will undoubtedly determine whether adrenochrome is present in tissue. Of course, it may be present only in abnormal pathologic states.

Chemistry. Adrenochrome is very unstable even when crystallized in the cold, in the

dark, and in the absence of oxygen. On standing, it turns to a brownish black insoluble pigment called melanin. It is soluble in polar and relatively insoluble in nonpolar solvents. Several stable derivatives of adrenochrome are known, including the monoxime, the monosemicarbazone (adrenoxyl), and the mono-*p*-nitrophenylhydrazone. When freshly prepared, adrenochrome crystals are red. On standing, the crystals slowly turn black. When the black crystals are ground with mortar and pestle, the original red color reappears. On making a solution, fresh adrenochrome forms crystal-clear red solutions. As adrenochrome deteriorates, the solutions become less clear and contain fine black suspended particles. It appears that the formation of insoluble melanin occurs on the surface of the crystal so that each granule consists of adrenochrome surrounded by a shell of melanin.

Physiologic Properties. Adrenochrome is an efficient hydrogen carrier in physiologic concentration.[52] With its oxime and semicarbazone, it is an excellent hemostatic substance as far as capillary hemorrhage is concerned. Adrenoxyl has been widely used for this purpose. Adrenochrome inhibits mitosis. This is apparently linked to its inhibition of carbohydrate metabolism.[18] Adrenochrome catalyzes the inactivation of catecholamines. It also increases glycogen formation. When added to perfused rabbit's ears, it prevents fatigue of the sympathetic nervous fibers to the vascular system.[31]

The properties of the stable derivatives differ in many respects from those of adrenochrome. Thus adrenochrome produces a characteristic distortion of the spider web[137] and can be detected in microgram quantities. Adrenoxyl has no specific effect on the web pattern. Adrenochrome is unstable, whereas the derivative is stable. Adrenochrome produces marked inhibition of in vitro rat brain metabolism,[138] whereas adrenoxyl (Girard treatment derivative) is comparatively inert.[139] Similarity of action can be assumed if it is known that the stable derivative is hydrolyzed in the body; however, this is not known yet. Fischer and Lecomte[43] found that adrenoxyl was not hydrolyzed to adrenochrome in the body. When administered to fasting persons, about one-quarter was excreted unchanged. Only rapid hydrolysis could reproduce the same effect as the administration of adrenochrome. A slow release would permit the body to clear the adrenochrome as fast as it was formed.

When administered to rats (2.5 to 10.0 mg.) there was a marked drop in temperature, the decrease and duration of response being much greater with the larger dosage.[32]

The toxicity of adrenochrome for rats depends upon the purity of the product. As the purity of the preparation has increased, the $L.D._{50}$ has become smaller. The most recent preparation had an $L.D._{50}$ of 5 mg./Kg. Cause of death in animals was respiratory paralysis preceded by dyspnea, micturition, clonic convulsions and exophthalmos. Before death, mice were apathetic. This quickly passed off and was replaced by progressive spasmodic clonic convulsions beginning in the hind legs. Walking was unco-ordinated. When disturbed, the mice hopped about, often leaping into the air and falling over backwards.[32]

Chronic administration of 1 mg. of adrenochrome/day to albino rats for 30 days markedly decreased weight gain. The rats developed typical clonic convulsions of the hind legs, but alteration between contraction and relaxation was slow and prolonged. This reaction increased in severity with treatment. After 12 days there was a period of considerable activity immediately following the injection, succeeded by an interval of marked apathy. Toward

the end, the muscular involvement was replaced by a state of pronounced apathy. The animals, throughout the experiment, responded to handling or other disturbances. The only constant gross visible change in the tissues was a scattered pigmentation of the omentum. The numerous miliary nodules in the omentum contained macrophages filled with brown granular pigment. Occasionally moderate arteritis was noted in the omentum and intestine. This is produced with extreme difficulty in rats with drugs.[97]

As well as being an antigrowth substance, adrenochrome has auxin properties.[15] In a concentration of 1:100, it caused variable physiologic disturbances and growth inhibition in the root tips of *Vicia faba*. Hoffer[57] also observed a differential growth inhibition of *Avena sativa* rootlets of young seedlings as compared to the shoot inhibition.

Action on Cerebral in Vitro Metabolism. According to Woodford,[138] adrenochrome inhibits the aerobic metabolism of glucose, pyruvate, succinate, and malate. There are multiple sites of adrenochrome inhibition, probably including reactions involved in hydrogen transport. It was impossible to prevent the inhibition with glutathione, ferrous sulfate, adenosine triphosphate, and nicotinic acid.

Electroencephalographic Changes. Szatmari et al[121] found that intravenous dosages from 10 to 50 mg. increased the bilateral paroxysmal abnormalities in the electroencephalographic picture of epileptics but had very little effect on the cortical focus. These changes were reversed by nicotinic acid.

Psychologic Action. A report by Hoffer et al[63] concerning the hallucinogenic properties of adrenochrome challenged the imagination of research scientists, who properly attacked the hypothesis as a test of its validity. Rinkel et al[110] attempted to repeat the experiment but used so-called stable adrenochrome instead of adrenochrome. (Chemically adrenochrome is unstable,[3] but commercial adrenochrome is one of the stable derivatives.) Failing to detect psychologic changes in their volunteers, Rinkel et al[110] suggested that adrenochrome itself was not the active substance but that adrenoxine, a suggested but not yet isolated derivative of deteriorating epinephrine, might be the substance. The lack of effect of the stable derivative is not difficult to comprehend. As has been shown earlier, one would expect similarity of behavior only if the stable derivative were known to be hydrolyzed very readily in the body. However, in the light of some more recent work that will be discussed in this report, there is some doubt as to whether this is the only explanation. Hoffer[61] found that changes induced in volunteers by adrenolutin were not evident to most of them, i.e., there was no insight that change had occurred. It is thus possible that investigators accustomed to mescaline and LSD phenomena, and using a similar approach with a new hallucinogen, would fail to detect changes that depended upon the insight of the subject. Adrenochrome produced vivid perceptual changes in 1 subject who had experience with hallucinogens by self-experimentation and who was most skilled in describing subjective experiences. Most subjects found little striking perceptual change. The investigators and family of the volunteers, however, did note changes not seen by the volunteers.

When given to epileptics, only slight changes were found; however, most of the epileptics were deteriorated chronic mental hospital patients who were unable to verbalize any type of description. Furthermore, epileptic patients do not react to drugs, e.g., mescaline, as do

other subjects.[30] In a few of the acutely ill epileptics, the drug reproduced some of the aura that normally preceded the epileptic attack. In 1 instance, a schizophrenic psychosis in a suspected epileptic person followed one hour after the injection of 25 mg. of adrenochrome. The illness lasted about four months while the patient was in the hospital, but recovery followed a course of insulin coma therapy. The diagnosis of schizophrenia in this person was made at one of the hospitals by psychiatrists who were unaware that the subject had received any drug. Schizophrenic subjects have not reacted to adrenochrome psychologically; this is not unexpected.[61] If such substances are already circulating within the schizophrenic person, the addition of more will produce relatively little effect. Finally, it is possible that adrenochrome, which is quite unstable, may exist in combination with several other oxidized metabolites.

Recently, Turner et al[125] have attacked the so-called indole theory of schizophrenia. This theory remains as untenable today as it has at any time in the past. The Saskatchewan group looked for indoles in the body related to epinephrine, because the indole nucleus appeared to be common to many hallucinogens. This appeared a useful way of directing the search for a possible schizophrenic toxin. They did not, at any time, enunciate any indole theory. No biochemist could suppose that all indoles are active in producing psychologic change or that all hallucinogens must be indolic in nature. Some indoles are therapeutic, e.g., reserpine and desoxyreserpine. Nevertheless, indoles that have properties ranging from plant hormones (auxins) to vasopressor substances (serotonin) to hallucinogens (LSD) comprise a most interesting group of compounds. Criticism of the indole theory by Turner et al[125] has little significance in the study of schizophrenia. All of their observations could conceivably be correct but would play little part; however, their reference to the work of Rinkel et al without reference to the more recent published work of Rinkel[110] and their attributing to Szatmari et al the statement that adrenochrome is not hallucinogenic are incorrect.

Schwarz et al[114] studied the effect of injecting hallucinogenic drugs into the ventricles of cats. Adrenochrome in doses from 125 μg. to 1 mg. produced states of drowsiness from which the cats were readily aroused. Sometimes the cats would remain motionless and stare into space. After 20 minutes, they became moderately insensitive to pain. Sensorium remained clear, and the cats were affectionate and responded normally to petting. Memory was intact, as the cats were able to seek out their favorite resting places. One male cat made frequent attempts to copulate with a female cat and once attempted to copulate with a comatose dog that was in the laboratory. Drowsiness remained for 24 hours. Electroencephalographic changes were 4 cycles/second slow waves, with low-voltage spike components spreading to the frontal regions and then diffusely over the brain. These effects were not reversed by serotonin (250 to 500 μg.) intraventricularly nor by nicotinic acid intramuscularly (25 mg.). Adrenolutin produced similar effects, which, however, were more nearly immediate and pronounced. Smaller dosages of adrenolutin were as active as larger dosages of adrenochrome. Stupor and catatonia similar to that described by de Jong[28] were observed when the cats would sit in odd positions with their eyes wide open and howl. They permitted their limbs to be placed passively in unnatural positions that resembled

waxy flexibility in human beings. In spite of the apparent trancelike state, sensorium was clear, and the cats could always be alerted readily.

ADRENOLUTIN

The addition of a strong base to epinephrine solutions causes the development of a transient yellowish green fluorescence.[102] Lund[88] prepared the substance in pure form and termed it adrenolutin. Adrenolutin is a bright yellow crystalline substance sparingly soluble in water and organic solvents, yielding a yellowish solution with a marked fluorescence. Solutions readily absorb oxygen and are decolorized.

On standing, adrenolutin slowly darkens, probably by the formation of 5:6:5′:6′: dihydroxy-NN′-dimethyl indigo. The monohydrate forms yellow prisms more stable than the anhydrous material.[54]

Adrenolutin is prepared by treating aqueous adrenochrome with alkali in the presence of sodium dithionite. It is then acidified with acetic acid. The yellow crystals are precipitated and are recrystallized from water containing dithionite.

The properties of adrenolutin are very similar to those of adrenochrome, except that adrenolutin is generally more active, produces hypothermia in rats, is antimitotic,[44] and produces changes when injected into ventricles of cats. It, however, differs in other respects: Instead of producing inhibition of cerebral in vitro respiration, it may accelerate the uptake of oxygen[139] and is about twice as active as adrenochrome, as shown by its toxic properties, hypothermic effect, and by the results of intraventricular injections in cats.

Psychologic Properties. This was studied by administering 50 mg. of adrenolutin by mouth to paid volunteers, consisting of university students, nurses, physicians, and technicians. The volunteers were in good physical and mental health and were not emotionally disturbed at the time of the experiment. A double blind design was used.[61] This experiment is still under way. The description of the psychologic action of the drug is based on approximately 12 experiments from the design described and on 10 others from previous studies in which adequate dosages were determined.

Clinical Changes. During the double blind procedure, it was most difficult to predict whether the subject had a placebo or adrenolutin for the first run. This was not unexpected. Drugs such as mescaline and LSD impose such a characteristic pattern upon the subject that it is simple to detect whether active substances have been administered. However, anxiety may stimulate even LSD changes.[1] Adrenolutin does not impose a characteristic change upon the volunteers but, by interfering with basic thought and mood processes, allows each individual to react in a unique and unpredictable way. However, after the subject has shown during the first experiment how he reacts either to placebo or to adrenolutin, it is much simpler to predict correctly whether he has received the placebo or drug in the second experiment.

The predictions were made difficult by another factor. Adrenolutin is a possible metabolite of epinephrine. Therefore, if in any volunteer there is a substantial conversion of epinephrine to adrenolutin, that subject may react as if adrenolutin has been administered

to him. Feldberg and Sherwood[42] have suggested that extreme fatigue associated with marked and sustained anxiety might be associated with overproduction of epinephrine, with some permeation into the central nervous system. This seems a quite reasonable hypothesis. Some of our volunteers, especially during the first experiment when their situational anxiety was most acute, were thought to have received adrenolutin. It is quite interesting that very few receiving adrenolutin in the experiments were thought to have received the placebo but that many receiving the placebo were thought to have received adrenolutin. In spite of these difficulties predictions in the entire group were made at the 10 per cent level of probability after the completion of one quarter of the experiment (13 subjects). Maintaining the same level of accuracy, the possibility that this prediction was due to chance would drop below 1 per cent.

Another factor is that some subjects will be nonreactors. In biologic experimentation, a certain proportion of the population are nonreactors, due to factors such as rate of absorption from the intestine, innate resistance, and other variables. With LSD, 2 out of 10 subjects did not show any response to 100 μg.

Thought Disorder. This is extremely difficult to define and to measure either clinically or by psychologic testing. The clinical assessment of thought change and of the over-all psychologic change as measured by tests appears slightly more reliable than psychologic change alone as measured by tests. This is similar to the findings in Tyler's[126] sleep deprivation study in which after 40 hours all normal subjects developed psychotic-like changes but even after 120 hours no psychologic tests reliably detected thought disorder. The changes became apparent away from the experimental situation, for example, during dinner or marches when the soldiers were not in any test situation; they were most noticeable in the evenings.

Thought disorder was measured by engaging the volunteer in a severe and critical discussion about subjects pertaining to his own field of interest. The investigators were deliberately hostile, difficult, and antagonistic. As the subjects became hostile, they were able to participate in the argument less effectively. In addition, the electroencephalographic technician was simultaneously attaching the electrodes, which was quite distracting to the subjects. During placebo runs, the subjects did well during debate. During adrenolutin runs, the subjects became irritable or hostile, and they found it difficult to present adequate arguments. Some withdrew from the situation by giggling, becoming silly, questioning the motives and good faith of the investigators, or by bringing up circumstantial evidence. With 1 subject, a graduate nurse, the merits of an increase in salary were discussed. The investigator pointed out that nurses were already earning too much and that they were using nursing as a stopgap until marriage, which usually occurred shortly after graduation. This subject was quite euphoric and giggly, although normally a reserved, shy, rather quiet girl. After some thought, she remarked: "We were told by a speaker recently that all nurses are frigid and therefore do not get married." This was clearly out of character for her. The next day she was unable to account for this statement. During the placebo run, she was able to defend her point of view quite well by using appropriate arguments. Other subjects thought the investigators were silly and were irritated by them. One subject was

bored and became fatigued by the argument. A week later with use of the placebo, she relished the argument, thought it most enjoyable and interesting, and found the intellectual challenge very stimulating.

With some subjects, discussions on topics with which they were very familiar produced no evidence of thought disorder. This made it especially difficult for the investigator, especially since some subjects were more sophisticated in certain areas then the investigators were.

The use of proverbs was very useful for the detection of thought disorder in that most subjects receiving adrenolutin failed to comprehend the meaning of proverbs or, if they did comprehend the meaning, were unable to explain it. Some subjects refused to define the proverbs or defined them by quoting back another proverb. One subject felt she understood the meaning of the proverb but disagreed with its meaning. With use of the placebo, the subjects had little difficulty with proverbs, and no bizarre responses were obtained. The subject who disagreed with the meaning of proverbs while receiving adrenolutin did not disagree when receiving a placebo. Matched but different proverbs were used for each experiment.

With use of adrenolutin, some unusual responses were obtained; for example, a graduate student in physics felt that the proverb "a stitch in time saves nine" referred to some unit of time, that is, that "stitch" was a unit of time. He was unable to explain this proverb until it was read to him as "a stitch in time saves nine stitches." The proverb "many hands make light work" caused him to burst into laughter and to reply that it reminded him of his children's handprints on the wall.

Proverbs were also useful in that one could pounce upon any unusual response and, by encouraging the subject to elaborate, bring out thought disorder more clearly.

Problems in calculation were also used, for example, the serial seven test. With adrenolutin, subjects made more errors until the errors were brought to their attention, after which they were able to perform this test correctly. One subject who was unable to do this correctly was surprised as she enjoyed mathematics; the following week on a placebo run, she was able very rapidly to perform the serial six and seven test without any difficulty. On the adrenolutin run, she was unable to work out medical dosage problems in grains but was able to do so in milligrams. Her basic training had been in the avoirdupois-weight system, but she was now teaching undergraduates to make conversions daily. To give an example of her confusion, after it had been established that 30 mg. was equivalent to half a grain, she replied, on questioning, that she would hesitate to give a patient half a grain of morphine because it appeared excessive; in the same breath she reported that she would not hesitate to give a patient 30 mg. of morphine because "this was not very much." A week later on the placebo run, the subject was extremely fluent in all conversions, and it was impossible to confuse her.

The comprehension and similarity items of the Wechsler-Bellevue intelligence scale are most useful in picking up thought disorder. For example, 1 subject receiving adrenolutin reported on the similarities test that an orange and a banana were similar because they had skins and contained material inside the skins. When asked how a wagon and bicycle

were similar, she reported that they had wheels. The same subject when receiving a placebo was able to grasp the similarities quite readily. The next day after receiving adrenolutin, she did not understand why she had been unable to detect the similarities since she now knew what they were. A physician reported that the eye and the ear were similar because they were both on the head and that a lion and dog were similar because they had fur. When receiving adrenolutin, subjects were less voluble and quieter, and conversation became more of a question-answer type. On the placebo run, this tendency was not as great: the subjects were more spontaneous in their comments and asked more questions about the purpose of the experiment. It was more difficult for the subjects to describe their feelings and to describe the visual patterns while under the impact of the stroboscope. Many complained of thought disturbance and thought slowing and felt they were not doing as well as they should do, but this was also found in some placebo experiments.

Memory, orientation, and consciousness were normal. The next day most subjects were able to recall the experience, with 2 exceptions. One felt as if the experience had occurred three months before and the other subject who could normally reconstruct an evening's conversation was unable to do so for the evening of the experiment. This did not occur after placebo administration. A third subject during the second experiment (placebo) ascribed an error to the investigator which she herself had made during the first experiment (adrenolutin).

Many subjects receiving adrenolutin became suspicious and showed referential thinking. This has occurred in 1 subject receiving a placebo. Many become sensitive to experimental scrutiny and were aware of the fact that they were being closely observed. This feeling is much less intense or nonexistent with use of a placebo.

In 2 cases, adrenolutin has produced disturbances in sleep. In 1 instance, the subject had a most unusual dream with a nightmarish quality; she dreamed that there were furry animals nestling against her neck.

One subject receiving adrenolutin was rather subdued but very cooperative. The experimental team, in trying to assess the presence of thought disorder, asked him his views on socialized medicine and tried to engage him in an argument. However, he refused to argue and instead agreed with every point the team made. The team felt at the end of the experiment that there was some slowing of thought but that it was not marked. All the changes noted were accountable on the supposition that the subject was merely anxious (the first experiment) and that he had received the placebo. They were wrong in their prediction as he had received adrenolutin. After the subject had finished both experiments, he finally came and confessed that he had not told exactly what had happened during the first experiment and reported the following facts. When the investigator had asked him his view on socialized medicine, he suddenly became aware of the fact that both investigators were communists. This was surprising to him as he had known one of the investigators before and had not suspected this. However, this investigator now appeared quite sinister. An element of doubt remained, and he determined that he would try and obtain more evidence as to whether these truly were communists. He felt that the experimenters were asking him all these questions in order to try and draw him out and to trap him. How-

ever, he now felt quite superior to them both intellectually and knew that he could play that game much better than they. He decided to play along with them and to agree with whatever proposition they put to him, and he knew that in this way he would finally obtain convincing evidence. This went on about one hour. At the end of the time, he noted that one investigator was using a pencil labeled "Province of Saskatchewan." When he saw this, all his doubts were resolved, as he definitely knew that only a communist could have obtained access to this pencil. Shortly after, the electroencephalographic run was started, and he lost this train of thought. The next morning, the experience was vivid in his mind, and he could not understand how this "ridiculous" idea could have possessed him. However, he felt too ashamed to report the unusual experience. During the placebo run, there was no change in him whatever, and he was intellectually better than in the previous experiment. He did not develop any sign of thought disorder. This is a most interesting event in that it illustrates a development of a paranoid thought disorder and elaboration and illustrates how the clinical team was unable to make a correct prediction because the subject withheld ideas present during the experiment. The subject felt guilty about this for some time, and, only after he had been told that he had been given the drug in the first experiment, did he relate the story.

Anxiety. Anxiety is very difficult to quantify, but this has been done by noting the subjective reports and by looking for the usual physiologic concomitants of anxiety. The entire experimental situation was suitable for the production of anxiety. Before the experiment, the subjects had been informed that changes would be minimal and that perceptual changes would be nonexistent. However, all volunteers knew they were participating in a schizophrenia research program in which the drugs used might reproduce some of the phases of schizophrenia. They were called a few days before the experiment and given printed instructions, as well as bottles for urine collections. By the time they arrived at the laboratory, especially for the first experiment, most of the subjects had anxiety, which they felt subjectively and which was evident to the investigators. After the administration of the placebo, the anxiety decreased or increased but at no time disappeared. In some instances, the anxiety was so intense that after three hours the subjects became quite fatigued. In all subjects receiving adrenolutin there was a remarkable reduction of anxiety within one-half hour after its administration. In some cases, the subjects appeared quite flat, whereas previously they had been very anxious. The decrease in anxiety was manifested by feelings of relaxation, by spontaneous comments that they felt very much at ease, and by their calm relaxed attitude. When the anxiety was very high at the beginning of the experiment, the change was most dramatic. When anxiety was low at the start, it was difficult to detect change.

The stipple test[103] was developed in Holland in order to differentiate between hysteria and epilepsy and has recently been used to bring to light latent cases of epilepsy. It consists of a long sheet of paper containing 50 lines of groups of three, four, and five dots. The subject is instructed to cross out the groups containing four dots. The time required to complete each line is recorded by a stop watch. The test is analyzed by counting the number of errors and omissions and by determining the standard error of the mean time required

to complete one line for the first 25 lines as compared to the second 25 lines. This provides measures of the variability of time required to complete lines of the first and second halves of this test. Under the influence of adrenolutin, the standard deviation of the second half was lower than that of the first half (in 10 out of 11 experiments). With the placebo, the reverse occurred (11 out of 15 experiments). At first, this appeared to be a specific adrenolutin effect. However, a series of normal people were tested without warning, so that they would not build up any anxiety. The majority responded as if they had had adrenolutin. Thus, normal unanxious persons did better during the second half of the experiment, whereas normal persons who were anxious as a result of participation in the experiments did better in the first half. The changes are statistically quite significant. The subjects given adrenolutin reacted as if they were normal, i.e., without anxiety. It is likely that the adrenolutin, by removing subjective awareness of anxiety, permitted the subjects to perform the stipple test in a normal way. With respect to errors and omissions, the fewest errors were made by normal persons free of anxiety, the next fewest by normal persons with anxiety, and the fewest after that by normal persons receiving adrenolutin. Thus, in spite of the decrease in subjective anxiety, the subjects receiving adrenolutin were not able to perform as well, using errors and omissions as criteria.

An interesting dissociation occurred between clinical anxiety on one hand and intellectual performance and electroencephalographic anxiety on the other hand. Some placebo subjects showed great anxiety throughout the experiment but on the electroencephalographic run were relaxed and, in general, showed great interest and no intellectual impairment. The same subjects with use of adrenolutin showed no anxiety at all, but intellectual performance was deteriorated and on the electroencephalogram they showed an anxious type of pattern, that is, a low amplitude, high frequency pattern quite different from the previous placebo pattern. This has been observed in many subjects. There does appear to be a dissociation, as if the anxiety is still present but no longer noticeable to the subject. It is possible that adrenolutin destroys insight for the presence of anxiety, which is still present and seen on the electroencephalographic tracings. Of course, this may be an electroencephalographic pattern specific for adrenolutin.

Mood. Mild but clear changes in mood were produced by adrenolutin. Usually these were depressive in character and accompanied by increased irritation. These occurred within the first two hours of the experiment and were always present during the second half of the experiment. A few subjects in the first half of the experiment showed silliness and euphoria, which was later replaced by depression. One subject showed euphoria the first two hours and depression the second two hours; when she arrived home that evening, she again showed marked euphoria, silliness, and hypomanic behavior. After completing both experiments, most subjects selected the placebo as the most effective euphoriant.

Level of Interest. This was determined by the spontaneity of the subject, the number of questions asked regarding the experiment, and the willingness of the subject to elaborate on his experiences and to participate in the various tests. With use of the placebo, the level of interest usually remained very high, although in a few instances it began to decrease after about three hours. When the level of interest was markedly down during the per-

formance of any particular test, it was easily reawakened by conversation. With adrenolutin, most subjects became disinterested by 7 p.m. and more often found the tests boring. Their level of interest did not reawaken as readily, although in a few cases by 10 p.m. they once again became more interested in the experiment. Some subjects stated that they were quite disinterested in the whole experiment. Many stated that they were interested but appeared quite withdrawn from the situation. With use of the placebo, the subjects were anxious to perform well and were quite critical of their performance; with adrenolutin, the subjects were less critical of their performance and performed many of their tests with an increased number of errors.

Sociability. In an experimental situation in which the subject does not know the investigators, certain patterns of behavior are accepted. Under the placebo runs, no incongruity was determined, but under the adrenolutin runs quite often the subjects were critical of the experimenter, found the experiment silly, could find no reason why certain tests were being done, or came out with inappropriate sexual comments. This was used as evidence of social disinhibition, and, in 1 instance, this continued in a subject for two to three days. It was noted by her friends that she showed little empathy and most unusual behavior.

Visual Changes. Visual changes were mild and were not reported spontaneously except by 1 subject receiving the placebo subject. As a standard test, the subject was asked to look at a spinning Archimedes' wheel in which the lines appear to move outward. During the afterimage, the lines appear to move inward. One subject receiving adrenolutin saw the disc moving toward her when it was spinning, and during the afterimage she saw it move away from her. With the placebo, she saw it in the normal way. Other subjects have noticed difficulty in seeing lines.

When the subjects were exposed to the stroboscope, they saw vivid colors and geometric patterns, with use of both the placebo and adrenolutin; however, with adrenolutin, the colors were more vivid and the patterns less geometric and much more disorganized. In a couple of instances, clear-cut images were seen. For example, 1 subject saw pairs of eyes of different sizes, perfectly matched with the eyelids, without eyebrows and face, moving across the field in a clockwise direction. The eyes were very bright, pleasant, and very real. When receiving the placebo, she did not see these eyes. Another subject saw the redwood trees of the Pacific Coast with the sun glinting on them. In many cases, the stroboscope produced strong feelings of unreality. One subject receiving adrenolutin felt that he had just seen a nightmare in technicolor. Very often, the flashing light interfered with thought processes and made it difficult to describe the visual pattern. This, however, has occurred in some subjects receiving the placebo. The subjects usually found the stroboscopic experience more exciting when they had taken adrenolutin.

Other Changes. Feelings of unreality occurred; for example, 1 subject said he felt dizzy and added, "It is like being dizzy but suffering from none of its effects." Another subject complained she had a fuzzy feeling in her head and found it difficult to focus on things. Another felt numbness in his right leg as if it were going to sleep, but after walking around on it for some time he noticed no change. When looking at the stroboscope, he felt as if he had two independent eyes looking at the visual field. Another subject complained that her

head felt dull. Still another reported that he felt quite strange and had a similar feeling only once during the war when he had been on guard duty for 36 hours without sleep. Some subjects compared the adrenolutin reaction to having taken a couple of alcoholic drinks. They did not notice any of the other effects that they had noticed with alcohol.

Insight. When volunteers are given hallucinogenic drugs, for example, mescaline or LSD, they observe vivid visual phenomena and usually have no difficulty in being aware of marked change. With mescaline or LSD, the subjective experiences are more striking than the objective changes. Other drugs that do not produce vivid perceptual changes may produce a change in the volunteer that is not recognized by him. Very few of the volunteers were able to detect whether they had been given adrenolutin. Many of them felt that the placebo was a more active drug, probably because they remained anxious throughout the evening and ascribed the anxiety to the drug rather than to the situation. It was impossible to predict from the subjective statements whether the volunteer had taken adrenolutin. The most common reply to the question of whether anything had happened was that nothing had happened with adrenolutin but that something had happened with the placebo. It became therefore important to disregard subjective statements of change and to use as much as possible objective criteria for change.

It is interesting that, where the subjects were aware of a change, they readily found explanations and excluded the possibility that it was due to the drug; for example, 1 subject did become quite free of anxiety one hour after taking adrenolutin and explained it as due to the fact that he was familiar with the situation and with the experimenters. Most subjects felt that the placebo was the more active euphoriant.

Neurophysiologic Changes. Critical flicker fusions were determined before and after the administration of the drugs, i.e., placebo or adrenolutin. A soft intensity light was used with the FFF running about 20/second. With use of the placebo, the FFF was highest at the time of the first testing; during the evening it gradually fell, with a mean decrease of 6 per cent at the end of three hours. With use of adrenolutin, the FFF fell for 30 minutes and then returned to its original value at the end of three hours. Using a decrease of greater than 2.5 per cent of the initial value as a criterion of placebo reaction, the FFF correctly predicted 18 out of 20 experiments. The action of adrenolutin in preventing FFF fatigue resembles the action of amphetamine and *d*-desoxyephedrine hydrochloride, both cortical stimulants. This may be due to some action on sympathetic centers of the visual cortical craters. Deroaux and Roskam[31] found that adrenochrome prevented fatigue of stimulated sympathetic vasoconstrictor nerves in rabbits' ears. Adrenolutin may be formed from adrenochrome in the body.

RELATIONSHIP OF ADRENOCHROME AND ADRENOLUTIN TO SCHIZOPHRENIA

As a working hypothesis, Hoffer et al[63] suggested that oxidized derivatives of epinephrine were etiologic factors in the genesis of schizophrenia. A unifying hypothesis was developed following the reasonings quoted by Woolley.[140] This hypothesis, developed by Hoffer and Osmond in 1955, has been most useful in developing a research program and in suggesting fruitful lines of investigation. It consists of the following consecutive equations: 1. Bio-

chemical constitution plus the unknown = autonomic change. 2. Autonomic change (initial) = increased parasympathetic activity. 3. Autonomic change (secondary) = increased sympathetic activity. 4. Epinephrine is detoxified via amine oxidase, sulfoesterase, and phenolase. This mechanism (phenolase) predominates in schizophrenia, with production of quinone indoles (adrenochrome and adrenolutin). 5. Quinone indoles interfere with cerebral metabolism. A useful hypothesis must unite a body of unrelated data into a simple satisfying relationship and must make predictions that can be verified in the laboratory. Common to all the equations is the prediction that any factor that will drive the reactions to the right will initiate or aggravate schizophrenia and that factors braking or inhibiting the reactions will be therapeutic.

The most interesting equations at the moment are the second, third, and fourth.

Equation 2. Autonomic disturbances are very frequently found in the schizophrenias, especially in the acute phases.[46, 47] According to this equation, the parasympathetic nervous system is heavily involved. Increasing the concentration of acetylcholine will aggravate or produce schizophrenia. Conversely, its reduction will be therapeutic. The administration of substances that elevate acetylcholine levels will be harmful to the schizophrenic. Injections of acetylcholine into the ventricles of cats produce catatonic-like muscular changes.[42] Injections into the ventricles of schizophrenics increase the severity of the illness.[90] If these are followed by acetylcholine esterase injections, the changes are rapidly reversed; injections of esterase into chronic schizophrenics with permanent intraventricular cannulas have produced interesting clinical remissions.[115]

When patients are injected with atropine, neostigmine, and acetylcholine,[59, 120] they develop interesting psychologic and electroencephalographic changes. Some schizophrenics developed a sleep electroencephalographic pattern without showing subjective evidence of sleep. Other schizophrenics developed little sleep activity but suffered a reactivation of earlier symptomatology. In normal persons sleep was produced on the electroencephalogram and subjectively, but, in epileptics who showed remarkable electroencephalographic changes, no sleep activity whatever was noted subjectively. This triad of drugs that produces sleep elevates parasympathetic activity, especially the nicotinic aspects, which produces an aggravation of the schizophrenic process. Neostigmine is an esterase inhibitor equal in potency to physostigmine (eserine), but without the central activity of eserine.[34] In private discussion, Elkes[33] suggested that eserine might be more active in the production of sleep activity. Eserine is an indole whereas neostigmine is not. On standing, eserine becomes reddish, with the development of rubeserine, a red derivative quite similar in structure to adrenochrome.[51] Preliminary experimentation[57] indicates that with use of eserine there are no somatic changes noted when acetylcholine is injected, i.e., no coughing or dyspnea, so that the patient is unaware of the injection. With use of neostigmine, the acetylcholine produces marked changes of very brief duration. Using eserine, the electroencephalographic changes are minimal until after the injection of the acetylcholine. Within a matter of seconds, however, marked electroencephalographic activity appears with slow high voltage activity similar to that described by Szatmari and Schneider[120] but much more intense and appearing much sooner.

If the concentration of acetylcholine is increased centrally, there might be some spillover into the other body fluids; this would necessitate, in the blood at least, increased concentration and activity of esterase to counteract the increased production of acetylcholine.[70, 105, 106, 109] Gellhorn found that serum of schizophrenics injected into rats produced a parasympathetic type of reaction.

Acetylcholine esterase inhibitors elevate acetylcholine concentration and, according to this equation, produce schizophrenic-like reactions. One of the best inhibitors is eserine, an indole alkaloid. The psychologic effects of eserine are difficult to determine as the drug produces toxic effects. It does markedly increase the epinephrine secretion from the adrenal gland. Another potent inhibitor of human pseudo and true cholinesterase is LSD,[123] a very potent hallucinogenic substance (Rinkel, DeShon, Hyde, and Solomon in 1952). Another substance exceedingly active in this respect is bufotenin,[38, 112] an indole found in *Piptadenia peregrina*, a plant used as an euphoriant and intoxicant by North American Indians since the days of Columbus. Another inhibitor is adrenochrome,[127] which has been discussed elsewhere in this paper. Intraventricular administration of adrenochrome and adrenolutin in cats produces trancelike states and animal catatonia similar to that described by de Jong.[28] Many indoles are effective esterase inhibitors, and some of these indoles are active hallucinogenic agents.

Another group of esterase inhibitors are the fluorophosphonates, e.g., tetraethyl pyrophosphate and di-isopropyl fluorophosphate. These both inhibit esterase, but this inhibition can be reversed by hydroxamic acids.[136] When used for the treatment of myasthenia gravis, they produce insomnia, terrifying nightmares, and hallucinations.[41] Intraventricularly, they produce scratching and catatonia in cats.[41] Rowntree et al[111] administered 1 to 2 mg. doses daily to depressives, normal persons, and schizophrenics. Marked changes were noted in normal persons and manic-depressives, but little change was noted in schizophrenics. The first two groups became depressed, but half the schizophrenic patients suffered reactivation of the psychosis.

Other esterase inhibitors[50] include morphine, atropine, amphetamine, phenobarbital, and caffeine; anesthetics also inhibit esterase.[35]

Equation 3. According to this equation, increased production of acetylcholine by stimulating sympathetic ganglions produces an increase in the secretion of norepinephrine and epinephrine. It therefore follows that this aggravates or induces schizophrenia, whereas inhibition or a decrease in the production of epinephrine is therapeutic. Injection of 1 mg. of epinephrine subcutaneously markedly aggravates the schizophrenic process in about half the patients[86] for a few minutes to several hours in duration. Norepinephrine forms adrenochrome with great difficulty,[19] whereas this formation occurs readily from epinephrine. Norepinephrine is not injurious therefore for schizophrenics and may even be beneficial. Blocking the conversion of norepinephrine, which occurs slowly,[9] would achieve two objectives: (1) a decrease in the production of epinephrine, and therefore of adrenochrome, and (2) a decrease in the production of norepinephrine and of acetylcholine by a push-pull principle.

Very few methyl acceptors are known.[25] One is nicotinamide,[69] which has some structural

similarity to norepinephrine. It is possible that the introduction of large quantities of nicotinic acid or nicotinamide into the body will, by competition for methyl groups that might be attached to norepinephrine by the proper enzymes, be therapeutic for schizophrenia. Nicotinic acid (Hoffer and Osmond in 1955) in doses of 3 to 10 Gm./day is a very useful treatment for most of the early schizophrenics and pseudoneurotic schizophrenics. More than 100 patients have been treated with and without electroshock, as compared to control groups receiving other treatment or a placebo. One year after discharge, schizophrenic patients admitted to psychiatric wards of general hospitals showed 80 per cent improvement, whereas in the control group about 35 per cent remained well. Nicotinic acid has no therapeutic effect on the great majority of chronic patients.

Both amide and acid are equally effective. This rules out the vasodilator action of the acid as the beneficial effect.[79] Furthermore, after a few days of continuous administration with nicotinic acid, the subjects no longer flush. Most striking are a small group of patients who require daily administration of the vitamin to remain well and who relapse within days to weeks after ceasing to take the vitamin. Some patients have been maintained in good health for three years with use of the vitamin when electroshock and other treatment had failed.

Equation 4. There is a very close and direct relationship between systolic blood pressure and the free concentration of epinephrine. Epinephrine is very toxic and must be destroyed by the body as fast as it is produced. There may be very little increase in blood concentration but an increased rate of turnover. In schizophrenia, the destruction, according to this hypothesis, results in the production of quinone indoles. This may be due to some defect in the enzymes that metabolizes epinephrine.[77] It follows that medications blocking the normal pathways of detoxification, amine oxidase, and sulfoesterase will produce or aggravate the schizophrenic process. Inhibitors of amine oxidase, when administered in excess, will produce toxic psychoses, e.g., cocaine, desoxyephedrine (which blocks both amine oxidase[9] and sulfoesterase[124]), amphetamine, LSD, morphine, caffeine, and atropine. Caffeine causes central excitation, insomnia, restlessness, and delirium when administered in large quantities.

Fluids of schizophrenics will contain increased concentrations of quinone indoles in the presence of normal concentrations of epinephrine. Adrenochrome and adrenolutin and blood serum to which epinephrine has been added for some hours are antimitotic substances.[44, 84] If, therefore, they are present in the blood, serum of schizophrenics will also be toxic to cells. Adrenochrome inhibits mitosis in mouse epidermis.[18] L strain fibroblasts originally obtained from mouse epithelial tissue are destroyed by serum of schizophrenics. Over 90 per cent of samples of blood from schizophrenics markedly inhibited growth of these cells.[39, 40] This toxic factor is heat labile. The toxin is not toxic for HeLa cell cultures obtained from human tissue. The toxin is not a virus, since there is a definite relationship to the amount of serum used. Serums may be diluted down until there is no toxicity whatever. The toxicity is greatest at the beginning of the growth phase. Occasionally cells survive and may produce flourishing cell cultures after about five to six days.

Indoles derived from the epinephrine metabolites ought to be present in blood and urine

of schizophrenics. In a large series of patients, Hoffer[57] found that specially treated wool adsorbed much greater amounts of substance from the urine of schizophrenics, concentrated during the night, i.e., the first morning specimen, than from the urine of nonschizophrenic patients. In the few instances in which normal persons contained the wool factor, it was entirely removed from the urine by the administration of chlortetracycline for two days, whereas chlortetracycline did not produce change in the wool factor of schizophrenics. This suggests that the wool factor in normal persons comes mainly from intestinal putrefaction, whereas this source of indole in schizophrenia is relatively unimportant. By direct staining of the wool factor, specific indole colors ranging from red to violet to dark blue were obtained (formation of indigo blue). The equation also predicts that adrenochrome and adrenolutin will produce psychologic changes. These have been discussed.

These are two basic conditions for the production of schizophrenia: an increase in the concentration and activity of acetylcholine centrally and an abnormal diversion of epinephrine into some quinone indole. Any substance that will block acetylcholine esterase and that will increase the production of epinephrine or its conversion into the indole, and that per se is an indole of the proper constitution, meets these two conditions and ought to be a powerful psychotomimetic substance. In table I some of the substances are listed that fulfill both these criteria.[36]

LSD and bufotenin appear to be the most potent hallucinogens. LSD, an indole, inhibits esterase and stimulates the production of epinephrine.[85] It is the most potent substance. Adrenochrome and adrenolutin are probably inhibitors of esterase and, in addition, may be present naturally in certain individuals. They are likely prototypes of the toxin of schizophrenics. Serotonin, a mild inhibitor,[76] produces a condition very similar to LSD intoxication in animals when 5-hydroxytryptophan is fed in large quantities[16] (converted into serotonin in brain). Tryptamine produces catatonia in animals.[98]

TABLE I

Some Psychotomimetic Substances

Substance	Dosage	Psychotomimetic properties	Esterase inhibition	Nature of activity
LSD	100 μg.	Strong hallucinogen	Strong	Indole, increases epinephrine production
Bufotenin	15 mg.	Moderate hallucinogen	Strong	Indole
Adrenochrome	25 mg. intravenously	Moderate schizomimetic	Medium	Indole
Adrenolutin	50 mg. orally	Marked schizomimetic	?	Indole
Eserine	?	Moderate schizomimetic	Strong	Indole
Serotonin	Intraventricularly	Moderate hallucinogen	Mild	Indole
Tryptamine	Orally	Moderate (catatonia)	Mild	Increases epinephrine production
Caffeine	Large	Moderate (euphoriant)	Mild	Increases epinephrine production
Mescaline	400 mg.	Strong hallucinogen	?	?

The series of equations show that the process may become self-perpetuating. Adrenochrome, which is an esterase inhibitor, will increase the production of acetylcholine, which will in turn increase the production of epinephrine and the formation of adrenochrome. Waelsch and Rackow[127] pointed out that eserine and adrenochrome were similar in structure and reported that 10^{-6} M of eserine produced 50 per cent inhibition of esterase compared to 10^{-4} M of oxidized epinephrine (not pure adrenochrome, since other oxidation products are undoubtedly present). Waelsch and Rackow suggested that ". . . under physiological conditions, metabolic products of adrenaline may be formed which have a strong inhibiting effect on choline esterase. Formation of active oxidation products of adrenaline would not only result in a disappearance of adrenaline *per se* but also, by inhibition of esterase, in a slower removal of acetyl choline." Waelsch's supposition is built into the series of equations outlined.

After Hoffer et al[63] suggested that adrenochrome or some similar substance might be causally related to schizophrenia, Altschule[2] suggested that "an interesting hypothesis can be created to the effect that although prolonged excessive production of epinephrine might result in tolerance of its somatic effects, it might under some conditions cause the accumulation of toxic substituted quinones or related substances that cause psychosis by adversely affecting cerebral function."

Adrenolutin has a remarkable effect on subjective anxiety within 30 minutes after oral administration. Anxiety appears to be present and may account for the deteriorated intellectual performance. This raises an interesting theoretic problem regarding the role of epinephrine and its oxidized derivative in the maintenance of homeostasis. According to Cannon[24] epinephrine plays an emergency role in preparing the body for fight or flight. The increased production of epinephrine prepares the body physiologically, but its overproduction may be harmful in producing toxic changes. In human beings, the production of too much anxiety defeats the purpose of the preparation for the emergency reaction. If the conversion of epinephrine to adrenolutin does occur, it will provide a natural safety valve against the overproduction of epinephrine by decreasing the subjective awareness of anxiety (as does the administration of adrenolutin) and by changing the thinking process of the individual from an abstract to a concrete form. It is likely that, in emergency situations requiring intense effort, the ability to think in abstract terms is detrimental. The degree of subjective awareness of anxiety therefore depends upon the ratio of epinephrine to adrenolutin production. It follows that in the presence of large quantities of adrenolutin, the individual will not be aware of anxiety. The schizophrenic person who is not anxious when his disease is well established has solved the problem of the overproduction of epinephrine only too well. This postulate is testable by determining whether epinephrine produces anxiety in subjects previously treated with adrenolutin and by determining whether adrenolutin will remove anxiety from the acute anxiety state (the price may be temporary schizophrenia).

During the early phases of schizophrenia, before the process is well established, there will be phasic alterations, depending upon rates of conversion, during which the individual will suffer acute anxiety. When the quantity of adrenolutin builds up to a sufficient level,

anxiety no longer will be felt. During recovery, anxiety once more becomes noticeable to the schizophrenic patient. This may explain the clinical observation that many schizophrenic patients during recovery often appear to be suffering reactivation of their psychosis.

Chemically, it may be possible to measure the degree of anxiety by measuring in the urine the total daily output of epinephrine sulfate or aldehyde (the result of amine oxidase and sulfoesterase activity) and of epinephrine indole (result of phenolase activity). Anxiety will be marked by a high ratio of the first group of derivatives compared to the second group, and schizophrenia will be marked by a very low ratio.

Clinical Description of Schizophrenia from the Hypothesis. Any competent physiologist given these equations and a description of the properties of adrenochrome and adrenolutin would give the following summary of the changes to be found in schizophrenia. (This makes an interesting intellectual exercise and of course involves a prediction by a biochemical psychiatrist working with schizophrenia of what a physiologist, not knowing schizophrenia, would predict. 1. In schizophrenia there will be some autonomic nervous system disturbance, both parasympathetic and sympathetic. 2. There will be some disturbance of epinephrine metabolism. 3. Inhibition of amine oxidase will aggravate schizophrenia and produce toxic psychosis. 4. Schizophrenics' blood and cerebrospinal fluid will be toxic for L strain fibroblasts. 5. The rate of deposition of melanin pigment will be accelerated after the disease becomes established.[77] 6. Schizophrenics will suffer few allergies during their illness,[77] but their illness may alternate with any allergic illness such as asthma. 7. Schizophrenics will suffer little anxiety when the disease is well established. 8. Schizophrenics will tolerate huge quantities of histamine[87] (adrenochrome has antihistaminic properties).[67] 9. Urine of schizophrenics will contain unusual metabolites of epinephrine, perhaps indolic in nature. 10. Schizophrenics will tolerate huge quantities of thyroxine (quinones are antagonists to thyroxine). Further, the basal metabolic rate will be lowered without any change, or even with elevation of protein-bound iodine, since adrenochrome is antagonistic. Thyroxine inhibits the activity of amine oxidase and produces anxiety or even schizophrenic-like psychosis. Thus increased production of thyroxine will increase the production of adrenochrome, which, in turn, increases the tolerance for thyroxin. 11. Psychologically, the description of adrenolutin already given will suffice as a description of early schizophrenia. 12. In children there will be major growth disturbances[5] since adrenochrome in rats prevents normal growth.[32] In adults, the more rapidly growing tissues may be most affected by the disease. Perhaps there will be a decreased rate of growth of hair, of nail, and of testicular function. Rate of fibrosis and of healing will also be slowed, which may account for increased prevalence of tuberculosis. I have observed a schizophrenic child who required no haircut for the first three years of life and who suddenly required frequent cuts and showed clinical improvement after the administration of nicotinic acid.

SUMMARY

There is a close relationship between mental disease and the autonomic nervous system. Norepinephrine, the sympathetic mediator, appears to have little direct emotional com-

ponents. Epinephrine plays a vital role in emergency reactions and anxiety states. Two oxidized derivatives of epinephrine, adrenochrome and adrenolutin, when administered to normal volunteers, produced changes in thought and mood, with or without perceptual changes, that in many ways resembled those found in early schizophrenia.

Although direct evidence that these substances are present in the schizophrenic person is lacking, there is a great deal of indirect evidence for this possibility, and enzyme systems that in vitro do effect the conversion of epinephrine to adrenochrome are present in vivo. It would be quite astonishing if this change were not found in vivo.

Adrenochrome and adrenolutin are both antimitotic factors for L strain fibroblasts, and schizophrenic blood (which may contain these substances) is also toxic. Unusual indoles are possibly present in the urine of schizophrenics. Epinephrine is converted by blood of schizophrenics into a fluorescent substance. Both substances produce catatonia and other changes when administered intraventricularly to cats.

The hypothesis is developed that in schizophrenia both branches of the autonomic nervous system are overly active as a result of an overproduction of both acetylcholine and epinephrine. The changes suggested by this hypothesis are reviewed in the light of present information. It is suggested that this is a reasonable, unifying hypothesis that will prove useful in obtaining more information about schizophrenia.

ACKNOWLEDGMENTS

This research was made possible by generous contributions of adrenolutin from Dr. J. Harley-Mason, Cambridge, England, and from Dr. D. E. Hutcheon, Chas. Pfizer & Company, Inc., New York, N. Y. The great intellectual stimulus obtained by discussing the subject matter of this paper with the members of the Saskatchewan Committee on Schizophrenia Research was most helpful. I am especially grateful for the tremendous assistance received from my colleague, Dr. H. Osmond, Superintendent, Saskatchewan Hospital, Weyburn. The final hypothesis has been a conjoint work of four years' duration in which ideas have been so intertwined that it is impossible to know their origin.

RESUMEN

De acuerdo con este autor, la epinefrina desempeña un papel vital en las reacciones de urgencia y en los estados de ansiedad; dos derivados oxigenados de la epinefrina, adrenocromo y adrenolutina, producen cambios en el pensamiento y el humor que se parecen a los que se hallan en la esquizofrenia precoz.

El adrenocromo y la adrenolutina son factores antimitóticos para las cepas fibroblásticas L y la sangre de los esquizofrénicos (que puede contener estas substancias) es también tóxica. En la orina de los esquizofrénicos existen quizá indoles no corrientes. La sangre de los esquizofrénicos convierte la epinefrina en una substancia fluorescente. Ambas substancias producen catatonia y otros cambios cuando se administran a los gatos por vía intraventricular.

Se ha emitido la hipótesis de que en la esquizofrenia, ambos sectores del sistema nervioso

autónomo, son demasiado activos como resultado de una sobreproducción de acetilcolina y epinefrina. Todo ello sugiere que se trata de una hipótesis razonable y unificadora que será útil para obtener más información acerca de la esquizofrenia.

RESUME

Selon l'auteur, l'adrénaline joue un rôle capital dans les réactions critiques et les états d'anxiété, et deux agents dérivatifs oxydés de l'adrénaline, l'adrénochrome et l'adrénolutine, ont produit des changements dans la pensée et l'humeur ressemblant ceux trouvés dans la schizophrénie à son début.

L'adrénochrome et l'adrénolutine sont des facteurs anti-caryocinétiques pour fibroblastes type L, et le sang schizophrène (lequel peut contenir ces substances) est également toxique. Des indoles rares sont probablement présents dans l'urine des schizophrènes. Le sang des schizophrènes change l'adrénaline en une substance fluorescente. Les deux substances entraînent la catatonie et d'autres changements lorsqu'administrées par voie intraventriculaire aux chats.

On formule l'hypothèse que dans la schizophrénie les deux branches du système nerveux sympathique sont trop actives par suite d'une trop grande production d'acétylcholine et d'adrénaline. On fait la revue de ces changements. On suggère que l'hypothèse est raisonnable et prouvera utile pour obtenir plus de détails sur la schizophrénie.

BIBLIOGRAPHY

1. Abramson, H. A.; Jarvik, M. E.; Levine, A.; Kaufman, M. R., and Hirsh, M. W.: J. Psychol. 40:367, 1955.
2. Altschule, M. D.: New England J. Med. 251:476, 1954.
3. Bacq, Z. M.: J. Pharmacol. & Exper. Therap. 95:1, 1949.
4. Bain, W. A.; Gaunt, W. E., and Suffolk, S. F.: J. Physiol. 91:233, 1937.
5. Bender, L., and Helme, W. H.: A. M. A. Arch. Neurol. & Psychiat. 70:413, 1953.
6. Beyer, K. H.: Physiol. Rev. 26:169, 1946.
7. Blaschko, H.: Nature 145:26, 1940.
8. Blaschko, H.: Pharmacol. Rev. 4:415, 1952.
9. Blaschko, H.: Pharmacol. Rev. 6:23, 1954.
10. Blaschko, H.; Burn, J. H., and Langemann, H.: Brit. J. Pharmacol. 5:431, 1950.
11. Blaschko, H., and Philpot, F. J.: J. Physiol. 122:403, 1953.
12. Blaschko, H., and Welch, A. D.: Arch. exper. Path. u. Pharmakol. 219:17, 1953.
13. Boscott, R. J., and Bickel, R. J.: Scandinav. J. Clin. & Lab. Invest. 5:380, 1953.
14. Bradley, P. B., and Elkes, J.: J. Physiol. 120:13P, 1953.
15. Brauer, I.: Biol. Zentralbl. 70:152, 1951.
16. Brodie, B. B.: Joint Meeting of the American Psychiatric Association and American Association for the Advancement of Science, Atlanta, Ga., December, 1955.
17. Bulbring, E.; Burn, J. H., and De Elio, F. J.: J. Physiol. 107:222, 1948.
18. Bullough, W. B.: J. Endocrinol. 8:265, 1952.
19. Bu'Lock, J. D., and Harley-Mason, J.: J. Am. Chem. Soc. 73:712, 1951.
20. Burn, J. H.: Brit. M. J. 1:784, 1952.
21. Burn, J. H.; Hutcheon, D. E., and Parker, R. H. O.: Brit. J. Pharmacol. 5:417, 1950.
22. Burn, J. H.; Langemann, H., and Parker, R. H. O.: J. Physiol. 113:123, 1951.
23. Buscaino, V. M.: Proceedings of the First International Congress of Neuropathology, Sept. 8–13, 1952.
24. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, Boston, C. T. Branford Co., 1953.
25. Cantarow, A., and Schepartz, B.: Biochemistry, Philadelphia, W. B. Saunders Company, 1954.
26. Cantril, H., and Hunt, W. A.: Am. J. Psychol. 44:300, 1932.
27. Danielopolu, D.: Compt. Rend. Soc. de biol. 140:298, 1946.
28. De Jong, H. H.: Experimental Catatonia, Baltimore, Williams & Wilkins Company, 1945.
29. De Largy, C.; Greenfield, A. D. M.; McCorry, R. L., and Whelan, R. F.: Clin. Sc. 9:71, 1950.

30. Denber, H. C. B.: Psychiatric Quart. 29:433, 1955.
31. Derouax, G., and Roskam, J.: J. Physiol. 108:1, 1949.
32. Eade, N.: Masters thesis, Department of Physiology, University of Saskatchewan, Canada, 1954.
33. Elkes, J.: Personal communication, 1954.
34. Elkes, J.; Elkes, M. B., and Bradley, P. B.: J. Ment. Sc. 100:125, 1954.
35. Elliott, K. A. C.; Swank, R. L., and Henderson, N.: Am. J. Physiol. 162:469, 1950.
36. Erspamer, U.: Pharmacol. Rev. 6:425, 1954.
37. von Euler, U. S.: Brit. M. J. 1:105, 1951.
38. Fabing, H.: Personal communication, 1955.
39. Fedoroff, S.: Anat. Rec. 121:394, 1955.
40. Fedoroff, S.: J. Lab. & Clin. Med. 48:55, 1956.
41. Feldberg, W. S.: Lancet 268:900, 1955.
42. Feldberg, W. S., and Sherwood, S. L.: J. Physiol. 123:148, 1954.
43. Fischer, P., and Lecomte, J.: Arch. internat. physiol. 36:327, 1949.
44. Frederic, J.: Ann. New York Acad. Sc. 58:1246, 1954.
45. Gaddum, J. H.: Recent Progress in Hormone Research 4:291, 1949.
46. Gellhorn, E.: Physiological Foundations of Neurology and Psychiatry, Minneapolis, University of Minnesota Press, 1953.
47. Gjessing, R.: J. Ment. Sc. 84:608, 1938.
48. Goldenberg, M.; Faber, M.; Alston, E. J., and Chaigoff, E. C.: Science 109:534, 1949.
49. Goldenberg, M.; Pines, K. L.; Baldwin, E. de F.; Greene, D. G., and Roh, C. E.: Am. J. Med. 5:792, 1948.
50. Goldstein, A.: Fed. Proc. 7:223, 1948.
51. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, the Macmillan Company, 1955.
52. Green, D. E., and Richter, D.: Biochem. J. 31:596, 1937.
53. Guyton, A. C., and Gillespie, W. M.: Am. J. Physiol. 165:319, 1951.
54. Harley-Mason, J.: Personal communication, 1955.
55. Hsath, R.: Personal communication, 1955.
56. Himwich, H. E.: Brain Metabolism and Cerebral Disorders, Baltimore, Williams & Wilkins Company, 1951.
57. Hoffer, A.: Unpublished observation, 1954-1956.
58. Hoffer, A.: A. M. A. Arch. Neurol. & Psychiat. 71:80, 1954.
59. Hoffer, A.: J. Nerv. & Ment. Dis. 119:421, 1954.
60. Hoffer, A.: Discussion of paper by Cholden, L.; Kurland, A., and Savage, C.: American Psychiatric Association Meeting, Atlantic City, May 9 to 13, 1955.
61. Hoffer, A.: Joint Meeting of the American Psychiatric Association and American Association for the Advancement of Science, Atlanta, Ga., December, 1955.
62. Hoffer, A.; Osmond, H., and Kahan, I.: Unpublished observation, 1956.
63. Hoffer, A.; Osmond, H., and Smythies, J.: J. Ment. Sc. 100:29, 1954.
64. Holtz, P., and Schumann, H. J.: Nature, London 165:683, 1950.
65. Hoskins, R. G.: The Biology of Schizophrenia, New York, W. W. Norton & Company, 1946.
66. Hunt, B., and Wassersug, J. D.: New England J. Med. 249:1051, 1953.
67. Hutcheon, D. E.: Personal communication, 1954.
68. Hutcheon, D. E., and Parker, R. H. O.: Brit. J. Pharmacol. 5:604, 1950.
69. Johnson, B. C., and Lin, P. H.: J. Am. Chem. Soc. 75:2971–2974, 1953.
70. Jones, M. S., and Tod, H.: J. Ment. Sc. 83:202, 1937.
71. Kamman, G. R.; Freeman, J. G., and Lucero, R. J.: J. Nerv. & Ment. Dis. 118:391, 1953.
72. Keller, E. B.; Boissonnas, R. A., and du Vigneaud, V.: J. Biol. Chem. 183:627, 1950.
73. Kisch, B.: Exper. Med. & Surg. 5:166, 1947.
74. Landis, C.: J. Comp. Psychol. 4:496, 1924.
75. Landis, C., and Hunt, W. A.: J. Exper. Psychol. 18:505, 1935.
76. Langemann, H.: Helvet. physiol. et pharmacol. acta. 12:C28, 1954.
77. Lea, A. J.: J. Ment. Sc. 101:538, 1955.
78. Lecomte, J.: Arch. internat. physiol. 61:84, 1953.
79. Lehmann, H.: The Biology of Mental Health and Disease, New York, Paul B. Hoeber, Inc., 1952, p. 582.
80. Leimdorfer, A.: J. Pharmacol. 98:62, 1950.
81. Leimdorfer, A., and Metzner, W. R. T.: Am. J. Physiol. 157:116, 1949.
82. Leimdorfer, A.; Arana, R., and Hack, M. A.: Am. J. Physiol. 150:588, 1947.
83. Lettre, R.: Ann. New York Acad. Sc. 58:1085, 1954.
84. Lettre, H., and Albrecht, M.: Ztschr. f. physiol. Chem. 271:200, 1941.
85. Liddell, D. W., and Weil-Malherbe, H.: J. Neurol. Neurosurg. & Psychiat. 16:7, 1953.
86. Lindemann, E.: Am. J. Psychiat. 91:983, 1935.
87. Lucy, J. D.: A. M. A. Arch. Neurol. & Psychiat. 71:629, 1954.

88. Lund, A.: Acta pharmacol. et toxicol. *5*:75, 121, 231, 1949.
89. McChesney, E. W.: Proc. Soc. Exper. Biol. & Med. *71*:220, 1949.
90. McCulloch, W. S.: J. Nerv. & Ment. Dis. *119*:271, 1954.
91. Madison, L. L.: J. Clin. Invest. *29*:789, 1950.
92. Marrazzi, A. S., and Hart, E. R.: Joint Meeting of the American Psychiatric Association and American Association for the Advancement of Science, Atlanta, Ga., December, 1955.
93. Martin, G. J.: Biological Antagonism, New York, Blakiston Company, 1951.
94. Martin, G. J., and Beiler, J. M.: Arch. Biochem. *15*:201, 1947.
95. Martin, G. J., and Beiler, J. M.: J. Am. Pharm. A. *37*:32, 1948.
96. Martin, G. J.; Ichniowski, C. T.; Wisansky, W. A., and Ansbacher, S.: Am. J. Physiol. *136*:66, 1942.
97. Moore, D., quoted by Eade, N.[32]
98. Nievenhuysen, F. J.: Proc. Roy. Acad. Sc. *39*:1151, 1936.
99. Osmond, H.: Dis. Nerv. System. *16*:2, 1955.
100. Osmond, H., and Smythies, J.: J. Ment. Sc. *98*:111, 1952.
101. Page, I. H.; Taylor, R. D., and Prince, R.: Am. J. Physiol. *159*:440, 1949.
102. Paget, M.: Bull. d. Sc. pharmacol. *37*:537, 1930.
103. Palthe, P. M. Van Wulfften and Van Weeren, J. T.: Aeromedica Acta. *3*:127, 1954.
104. Pleasure, H.: A. M. A. Arch. Neurol. & Psychiat. *72*:313, 1954.
105. Pope, A.; Claveness, W., and Livingston, K. E.: A. M. A. Arch. Neurol. & Psychiat. *68*:425, 1952.
106. Ravin, H. A., and Altschule, M. D.: A. M. A. Arch. Neurol. & Psychiat. *68*:645, 1952.
107. Richter, C. P.: Life, Stress and Bodily Disease, Baltimore, Williams & Wilkins Company, 1950.
108. Richter, D.: J. Physiol. *98*:361, 1940.
109. Richter, D., and Lee, M.: J. Ment. Sc. *88*:428, 1942.
110. Rinkel, M.; Hyde, R. W., and Solomon, H. C.: Dis. Nerv. System. *15*:3, 1954; *16*:229, 1955.
111. Rowntree, D. W.; Nevin, S., and Wilson, A.: J. Neurol., Neurosurg. & Psychiat. *13*:47, 1950.
112. Safford, W. E.: J. Washington Acad. Sc. *6*:547, 1916.
113. Sayers, G.: Recent Progress in Hormone Research *4*:291, 1949.
114. Schwarz, B. E.; Bickford, R. G., and Lichtenheld, F. R.: Personal communication, 1955.
115. Sherwood, S. L.: Lancet *268*:900, 1955.
116. Sobotka, H., and Antopol, W.: Enzymologia *4*:189, 1937.
117. Soffer, L. J.: Recent Progress in Hormone Research *4*:291, 1949.
118. Stewart, G. H., and Rogoff, J. M.: Am. J. Physiol. *66*:235, 1923.
119. Swan, H. J. C.: Brit. M. J. *1*:1003, 1952.
120. Szatmari, A., and Schneider, R. A.: J. Nerv. & Ment. Dis. *121*:311, 1955.
121. Szatmari, A.; Hoffer, A., and Schneider, R.: Am. J. Psychiat. *111*:603, 1955.
122. Teague, R. S., and Wingard, C.: Fed. Proc. *12*:372, 1953.
123. Thompson, R. H. S.; Tickner, A., and Webster, G. R.: Brit. J. Pharmacol. *10*:61, 1955.
124. Torda, C.: J. Pharmacol. & Exper. Therap. *77*:123, 1943.
125. Turner, W. J.; Merlis, S., and Carl, A.: Am. J. Psychiat. *112*:466, 1955.
126. Tyler, D. B.: Dis. Nerv. System. *16*:293, 1955.
127. Waelsch, H., and Rackow, H.: Science *96*:386, 1942.
128. Wajzer, J.: Bull. Soc. chim. biol. *29*:237, 1947.
129. Weil-Malherbe, H.: J. Ment. Sc. *101*:733, 1955.
130. Weil-Malherbe, H., and Bone, A. D.: Nature *174*:557, 1954.
131. Weil-Malherbe, H.: J. Ment. Sc. *98*:565, 1952.
132. Weinstein, S., and Manning, R. J.: Proc. Soc. Exper. Biol. & Med. *32*:1096, 1935.
133. West, G. B.; Shepherd, D. M., and Hunter, R. B.: Lancet *2*:966, 1951.
134. West, G. B.; Shepherd, D. M., and Hunter, R. B.: Clin. Sc. *12*:317, 1953.
135. Wiedorn, W. S., and Ervin, F.: A. M. A. Arch. Neurol. & Psychiat. *72*:321, 1954.
136. Wilson, I. B.: J. Biol. Chem. *199*:113, 1952.
137. Witt, P.: Helvet. physiol. et pharmacol. acta. *12*:327, 1954.
138. Woodford, V. R.: Eighth Scientific Session, Western Regional Group, Division of Medical Research, National Research Council, Winnipeg, Manitoba, Canada, 1954.
139. Woodford, V. R.: Personal communication, 1955.
140. Woolley, D. W.: A Study of Anti Metabolites, New York, John Wiley & Sons, Inc., 1952.
141. Zeller, E. A., and Barsky, J.: Proc. Soc. Exper. Biol. & Med. *81*:499, 1952.

Diagnostics and Psychotherapy of Psychosomatic Diseases

L. van der Horst, M.D.

PSYCHIATRISCHE EN NEUROLOGISCHE KLINIEK
UNIVERSITEIT VAN AMSTERDAM
AMSTERDAM, HOLLAND

In recent years increasing emphasis has been placed in clinical literature on the relationship between mental life and somatic diseases. For example, thyroid dysfunction may lead to displacement of mental equilibrium, and disturbances of the pituitary body and other glands of the endocrine system may cause alterations in mood and behavior.

The physician with a knowledge of physics and chemistry will find nothing surprising in this. He will have learned from experience that it is not only drugs that influence the mental condition but also that a somatic disease can produce a so-called exogenous reaction in the form of a symptomatic psychosis. This means that the physician has to keep in mind the psychic as well as the somatic state of the patient. Medical treatment, therefore, develops in two directions, i.e., organotherapeutically (drugs, physiotherapy) and psychotherapeutically. These two forms of therapy reveal the complications of illness. Accordingly, in our country, many disturbances are studied cooperatively by psychiatrists and internists.

In many of the so-called psychosomatic diseases we have to deal with the autonomic nervous system and the endocrine functions, as in hypertension, vasomotor disorder, hyperthyroidism, anorexia nervosa, and migraine. We know that passage of products of secretion not only in the vascular system but also in the nervous system provides evidence of the intimate functional connection between somatic processes and mental life. Particularly the hypophysis, with its connections to the nuclei of the hypothalamus, has received increasing attention from neuropsychiatrists in recent years. The passage of products of secretion into the central nervous system (neurocrinia, Masson) provides evidence of the intimate functional relationship between the hypophysis and the diencephalon. There are other relationships not involving the endocrine system which are studied in this field. But it must be noted that in many cases the psychosomatic interrelationship concerns the endocrinologic sphere.

Manic conditions and depressive states can result from a strong influence of the hypothalamic pituitary system. A new problem is whether the converse is possible, i.e., whether the function of the hypothalamus or pituitary gland can be changed by a stress situation and cured by psychotherapy. Here we enter the field of modern psychosomatic research. Freud's attitude in this matter was one of marked reserve: a few analysts such as Deutsch, Ferenczi, and Simmel have claimed successes with such treatment. The following case illustrates the difficulty of making a diagnosis of a purely functional disorder of the diencephalon or one with a psychogenic component.

Case 1. A 21 year old woman was admitted to my department with the diagnosis of schizophrenia. Her general condition was very poor. In a few months her weight had dropped from 150 to 90 pounds. She had

no appetite and refused all contact. Her face was haggard and without expression; her speech—when she spoke at all—was monotonous. The whole picture was that of an autistic, apathic girl. The skin was dry, with fine wrinkles on the forehead; the pubic hair was normal but the axillary hair scanty. Menstruation had ceased, fatigue and loss of weight dated from this time.

The patient had been engaged to a man of about her own age, whom she had known from her school days, but had broken off the engagement. Two months before admission there was a reconciliation, but her condition continued to deteriorate. At that time she spent several weeks in bed; she was said to be suffering from a kidney inflammation. She recovered from this, but the fatigue and apathy continued to increase. Her refusal to take food frequently caused trouble at home. It was no longer possible to gain contact with her.

Clinical examination revealed many signs suggestive of an endocrine disturbance. The basal metabolic rate had dropped to −22 per cent; the maximal blood pressure was 95 mm. of mercury; the pulse rate 52/minute; the blood sugar curve was depressed and flattened; and the creatine excretion was high. The patient was suffering from a multiple endocrine hypofunction. In such pluriglandular hypofunction, a pituitary deficiency undoubtedly must be assumed to be the central cause. This assumption was confirmed by the results of further tests; the cholesterol content and total protein content of the blood were above normal.

Since pituitary deficiency was suspected, substitution treatment was prescribed. The patient received daily injections of ambinon, and her diet was regulated with great care. Despite this her weight fell from 93 to 79 pounds. The cachexia began to assume an alarming form. From time to time she had pseudohallucinations and delusions, and we began to suspect that this was a case of Simmonds' disease—hypophyseal cachexia with the well-known triad of symptoms (lowering of basal metabolism, amenorrhea, and cachexia).* If this were correct, the prognosis was fatal. The atrophy of the diencephalic system would then have attained such proportions that recovery would be out of the question.

Although clinically the patient presented a picture of genuine Simmonds' disease, her age (21 years) and hair growth pointed to the functional form, indicating need for investigation of her history. However, it was very difficult to gain contact with this girl, and therefore I decided to try cathartic treatment with the patient placed in a hypnoid state. In this way I was able to penetrate the structure of her condition and experiences.

She was the second of 3 children. For a long time she had been the youngest and was cared for and watched over by the mother. Her sister, 2 years older, was more independent. When the patient was 11 years old, the third child, a boy, was born. Until two years before the time of examination she had suffered from jealousy of her brother. She begrudged him the mother's care and felt that he had usurped her place. In the last few months before her illness this feeling had completely changed; she took her brother for walks, played with him, and was completely reconciled to the present state of the family.

She had no interest in her work; she had a steady job and earned a good salary, all of which she brought home. She remained dependent on her mother for everything. The mother, who was a capable commanding woman with strong principles, had a stifling effect on the infantile and occasionally playful temperament of the patient. In spite of this, the patient's life developed in an apparently satisfactory manner. She was healthy and intelligent and pleased at first with her rapid growth in the years of puberty; at the age of 19 she was a rather heavily built, well-formed girl. She often heard people in the street making remarks about her womanly figure, but it did not worry her at all.

She became engaged at an early age. This was more of a friendship dating from school days than the choice of a future husband. The boy was a few months younger than she; in addition, he was unemployed and rather "small minded." She was superior to him in intelligence and social position. What interested him actively was religion, and especially dogmatic problems. She objected when he engaged her in religious discussions in which he took the lead. She would evade him, giving no answer, so that the conversation came to an end and she could then joke and chat with him about everyday subjects.

---

* In an interesting study, Richardson and Riply draw attention to similar cases. They emphasize the importance of recognizing the psychic origin of cases of so-called Simmonds' disease. For differential diagnosis between Simmonds' disease and the pseudo form three factors are stated to be of importance: the patient's age, the hair growth, and the mental condition.

None of these things caused her any worry. What she did find very trying was the attitude of her future mother-in-law, who expected her to regard the home of her "school friend" as her own home and the mother-in-law-elect as her own mother. Her response to this was breaking the engagement. When she began to grow thin, her family thought she was pining for her fiancé. But after the boy returned, and the engagement was resumed, she continued to lose weight. For it was not grief at parting but anxiety about the future that was troubling her. The demands of her fiancé's mother made her understand that the future would be otherwise than her infantile imagination had painted it. Although full grown, physically adult, and intellectually well developed, she was emotionally still a child. Her engagement was a protracted comradeship; remarks in the street about her physically adult appearance did not consciously affect her. Her dawning maternal instinct found satisfaction in "spoiling" her brother, whom she had formerly hated from the time of his birth. But in spite of all this she remained a child, held fast in the powerful fixation on the mother. Into this world of undisturbed equilibrium came now the demand of the future mother-in-law that she should accept the consequences of growing up. She had formed a quite different idea of the world and the future. And her ego took fright at her own growing up with which it had not kept pace. Some deformation of growth was necessary before the ego could feel itself at home again in its bodily and social environment. The bodily factor predominated here. The body with all its organs, in particular those organs that represented the fact of her being a grown woman, were assimilated into the biologic substructure. The primary demand was deformation of the body. Whether this ego deformation was already preformed in the deformation of early childhood (i.e., the phase in which the mother played the central part), I shall not discuss here. Nor shall I deal with the question of the way in which constitution and experiences of early childhood interacted. The point that concerns us is that this girl was afraid of growing up. She was shocked to discover that she was physically mature and that the world was already expecting her to face the social consequences. She became distressed and ill, arriving at the hospital as an exhausted, asthenic girl with the weight of an 11 year old child. Her face was infantile; she did not menstruate; and, in her conduct and embarrassment, in her hidden longing for completion, she was living again through the prepuberal period of the very young girl. Her somatic disorders were a manifestation of the life struggle with the too heavy task with which she was faced.

During the hypnoid catharsis her mental condition improved, she gained weight, and the imminent danger of a fatal outcome receded. As in the cases described by Richardson, the disease called for interpretation as a functional form of Simmonds' disease. The evidence for this was provided by the psychogenesis of the disorder, by the age of the patient, and by the absence of loss of hair. However, the course of this case still is not entirely clear.

The patient remained under follow-up for two years. With the agreement of the endocrinologist, I did not prescribe substitution therapy. One year after her discharge she began to menstruate again. Some months later there was no sign of endocrinologic disturbance.

In psychiatric literature such diseases are described as organ psychoses or organ neuroses (at any rate, as neurotic). Now, if we use the term "neurosis" or "neurotic," we have to bear in mind that the concept of neurosis has undergone changes. Formerly, a disturbance of function was termed "neurotic" whenever the observable bodily changes could not be accounted for organically. Nowadays the neurosis is seen in connection with the personal life history, and "neurotic" implies a term such as "psychogenetically nervous."

Janet used the term "psychoneurosis" and understood by this a mental disorder upon which the bodily manifestations (if present) were dependent. If there were bodily manifestations, the disturbances were called organ psychoses or organ neuroses. The psychoneuroses as well as the organ neuroses and psychoses, such as hypochondria, nocturnal enuresis, anorexia hysteria, and bronchial asthma, had in the opinion of Janet and his French contemporaries, or could have, a psychogenic etiology. Neuropsychiatry was built up in France and other continental centers, on the basis of these conceptions.

In Holland the previous generation had also placed psychiatry on a psychosomatic level. Nevertheless we got support from the new psychosomatic approach in the United States. In Europe, neuropsychiatry had attained an independence and its own place among the other medical specialties. During the war years it was found that the psychiatrist could make a considerable contribution to the health of troops. After the war the question arose of whether the psychiatrist could not make such a contribution to medicine and surgery in peacetime also. With this thought in mind, a system of cooperation was evolved between the psychiatrist and other relevant specialists. This psychiatric influence is strongly psychoanalytically oriented. Another orientation is held by psychophysiologic investigators who attempt to uncover the psychic influences on bodily suffering by biographic-associative examination. Their work is based on Cannon's principles of bodily changes in pain, hunger, fear, and rage. We know that the bodily tonus, the functions of the gastrointestinal tract, and the vasomotor tensions change when there is fear, anxiety, or anger. In our work we are not satisfied with this knowledge. The question arises of whether there is any specificity in the psychosomatic diseases. We are looking for a specific correlation, such as was attempted by Harold Wolff, Professor of Neurology at Cornell University. Wolff conducted several psychosomatic experiments on a man who had been fed through a stomach fistula, studying the condition of the gastric mucous membrane in different emotional states. Endoscopic examination revealed that each affect caused a specific condition of the mucous membrane; it either was inflamed, swollen, had much secretion, or was pale and thin. Each specific emotion caused a specific gastric condition. These biologic reactions lasted a short time and were, as such, harmless. But if they were continued or repeated several times, an unnatural situation arose that was no longer harmless. Not only functional disturbances but also anatomic lesions had been provoked. Now we know that most, if not all, of these biologic reaction patterns are related to the autonomic nervous system and the organs of internal secretion. But psychosomatic research is not content with this general knowledge. In all the so-called psychosomatic diseases, such as peptic ulcer, asthma, and ulcerative colitis, we are trying to determine the specific relationships; i.e., what is the stress situation provoking a certain reaction pattern, what is the psychic condition causing this stress situation to provoke a continuous emotional state, and what are the physical constitution and personal life history that caused this psychic condition? Our knowledge indicates that the psychosomatic disease has a specific origin in so far as a certain physical constitution and a certain personal life history are associated with a specific psychosomatic affection.

To illustrate what I mean, the following case histories, in which the psychic etiology is clear, are presented. They demonstrate another essential point: not only did the reasons for the emotional repression of inner conflict situations have a specific character in each specific disease, but also the specific personality structure and emotional conflicts were found to require special methods of approach for every disease.

Case 2. A 38 year old bookkeeper was referred to me by the Department of Surgery to determine whether he was suffering from a psychosomatic disease.

For more than six months he had been under a physician's treatment for gastric trouble. After diet and rest proved ineffective, and traces of blood remained a constant finding in the feces, he was admitted to the surgical

department, where a diagnosis of gastric ulcer was made. The professor of surgery requested a psychosomatic examination.

On examination we found a severely emaciated man who had worked hard all his life. Energetic, he had started his career as a junior clerk and gradually worked himself up to the position of senior bookkeeper. The father of six children, he had a strong sense of duty, was religious, and had always followed a strict moral code.

In his family he was the commanding father on the one hand and the spoiled husband on the other hand. On coming home, his glass of hot milk would be ready for him, and there was always some special treat for him. Although the size of his family was a source of worry, he always managed, by improving his position, to meet the demands of society. In the previous year, however, matters had become more difficult. His standing in the firm had suffered, and a younger man with better fundamental training threatened to overshadow him. In any case, he was now conscious of the fact that the supervisor, for more than a year, had seemed to discuss matters more with the young man than with him. In addition, after the birth of their sixth child 10 months previously, his wife was very weak and could hardly manage the house. She could not give him the extra attention he was used to. Now that the mother figure on which he had relied had fallen away, it became evident how dependent he really was. Along with his strong sense of duty, now emphasizing his struggle for life, this man had an urgent need for passive love. He had suffered two heavy losses: he had come into a conflict situation through frustration in his work, and this notwithstanding his energetic past, and he had lost the comforting love he so desperately needed. (In such cases we speak of the "double level" conflict, which we so often find in persons suffering from gastric or duodenal ulcer.)

We accepted this man for treatment, and in agreement with the surgeons no operation was done. He is now able to perform his duties again. (In this patient, as in all our cases, the elucidation of the mechanism of syndrome formation was a valuable guide in our therapeutic efforts.)

Case 3. An unmarried man of 28 years was admitted for treatment of bronchial asthma, which he had suffered from since 1946. A sister of his also had asthma. As a youngster he had always been very healthy, had good intellectual capacity, and had gone through high school without trouble. During the occupation, he was in the underground resistance movement and a member of a successful underground organization. In the beginning of 1945 he had to perform a heavy task with extreme exposure to cold. He succeeded, although he was always under enormous tension and in great danger. He associates his asthma with this nocturnal task. Psychiatric examination revealed that we were dealing with an extremely intelligent boy who came from a very religious family; his mother, at any rate, took religion seriously. His father tried to bring him up very strictly but had lost his son's confidence when it was discovered that he was seeing another woman, which caused his mother great suffering. His father did not allow him to go to the theater or motion pictures on religious grounds. In April, 1944, while attending a motion picture secretly one day, he saw his father and the woman in question two rows in front of him. A distrust developed from that time. In the underground movement he found the way to assert himself and to give expression to his desire for omnipotence. At home he was the favorite and at the same time the "comforter" of his mother, who discussed with him the infidelity of the father. His mother died suddenly on Dec. 25, 1944, and his father soon afterwards married the woman he had been seeing. She assumed a very authoritative attitude, and the home situation then became intolerable for the boy.

It was not until early in 1946 that the first signs of his disease appeared. This we have seen often. General experience has taught us that psychoneuroses take time to develop, and in the same way psychosomatoses also take time. But we must also remember that this boy had sufficient opportunity to satisfy his desire for omnipotence in the underground movement. Also, the resistance created an atmosphere in which he did not feel lonely any more. The loss of his intimate and comforting home with his own mother and the tyranny of his stepmother were less severely felt.

Toward the end of 1945 and the beginning of 1946 the resistance movement gradually ended. At that time, the symptoms of his asthma were manifested. He had been treated by various specialists with temporary success, but he always came back to his spray and his medicines, to which he seemed to have magical ties. He was admitted to hospitals on various occasions without any difficulty, because as an underground worker he had the right to receive support from the "1940–1945 Fund." He was attached to this support as much as he had been to mother care.

Eventually he was admitted to my clinic in the hope that I could divorce his disease from the experiences and hardships of the underground period and treat him on psychosomatic lines.

The principles we use in the psychotherapy of patients with various psychosomatic disorders, especially ulcerative colitis, peptic ulcer, and bronchial asthma, are partly the same as those used for the psychotherapy of patients with psychoneuroses and character neuroses. In addition, however, the specific personality structure and emotional conflicts present in patients with internal diseases have been found to require special methods of approach for every disease. Therefore, the concept of psychosomatic specificity not only has a value for the elucidation of the mechanism of syndrome formation but has also proved to be a valuable guide in our therapeutic efforts. The regression into more infantile attitudes that developed in these patients under influence of the disease and its consequences were considered in selecting the type of psychotherapy for the individual patient.

Both symptomatic, supportive forms, and deeper techniques of psychotherapy have been used, sometimes in combination with other therapies, relaxation exercises, interviews under thiopental, and group therapy. Working on this aspect, I was impressed by the importance of persistence as a factor determining the intensity of a patient's desire for cure or for a continuation of a rigid attitude. This may be elucidated by the following case history.

Case 4. A man suffering from ulcerative colitis was transferred from the medical clinic to my hospital. He was delirious, uneasy, and extremely emaciated, a living skeleton in a most deplorable state. He had frequent diarrhea with blood. He was difficult to nurse. Although he had been placed on a strict diet, my medical colleague withdrew all food restrictions, and we nursed him, tried to gain contact with him, and gave him (within certain limits) what he liked. After some days we began to feel that it might be possible to save this patient. In the interview he was childlike, explaining that he had a good economic position and a good business (a butcher shop) but that it was very crude, and that his wife, a butcher's daughter, was more spirited than he and had chaffed him many times because he was not more energetic. Her father was an ambitious man; he was head of a large shop and had under his supervision six assistants. The patient also felt inadequate in his marriage. There were no children. Further investigation revealed a homosexual factor in our patient. As a boy he was his mother's darling; when she died he lived with his sister's family, and a semihomosexual friendship developed with her brother-in-law. Despite this, he and his wife were good friends.

We treated this patient psychotherapeutically but also took into account his wife, the future care at home, and the possibilities in his job situation.

Three months after admission he was considered cured; he had no troubles with stools and no complaints, and he used, in emotional circumstances only, 10 to 20 drops of laudanum. He was discharged, although roentgen-ray examination with a contrast medium had shown that there were still gaps in the mucous membrane.

The patient remained under the care of one of my assistants and remained well for several months. Apparently we had had more success in the psychotherapeutic approach of an intestinal disturbance than internal medicine had had. But this patient was not cured completely—he persisted in his rigid attitudes.

He came back every week and attended a psychotherapeutic group session. Once he failed to come. The next day he was admitted to my clinic in a deep unconscious state following an attempt of suicide, in consequence of which he died.

The tragedy was first that he committed suicide with the very laudanum that he received from time to time from my assistants, but which he did not use, and secondly that the suicide took place on the evening of the missed group session. That evening his wife had suggested going to the theatre; she was bored staying at home every night. Her husband was slow and dull and not stimulating enough. He refused to go with her, arguing that he had to go to the group therapy session, although he had time to report his absence to us. She then phoned a friend, who went with her to the theatre.

When she returned her husband was sleeping very deeply, and she had no idea that he might have attempted suicide. When he did not awaken the next morning, she called the general practitioner.

In this case we have an infantile man with a narcissistic, introverted personality. Although married, he missed his mother and sister, an unbearable situation that he suppressed for years. In this way he created a continuous stress situation, causing biologic reaction patterns. Thus he found in his ulcerative colitis a slow way to an unobserved, unconscious suicide.

We, as physicians, always take a risk if we cure the symptoms of illness and do not cure the origin of it. In this case, we were pleased at curing a patient with ulcerative colitis who had been given up by internists, but our mistake was that we had cured only the symptoms —the patient found his way to death with our medicine. Here we are in the midst of the dynamics underlying psychosomatic problems.

The physician seeking to help a patient is repeatedly brought up against the problem of the reciprocal relationship between mental and bodily processes. In practice we take into account the fact that we are treating not merely a sick body but a whole person. We place a sufferer from tuberculosis in cheerful surroundings. In a case of serious disease we allow the patient to believe, whenever possible, that he has a chance of recovery. We know that recovery is greatly influenced by the mental state. But in practice it is very difficult to deal with these factors.

Being ill is not merely a casual event involving only the disease the patient has or reveals; it is not primarily a disturbed function or an altered structure, for we often find deviations from the norm in structure and function without the subject being ill. Being ill interferes with the course of our lives; it requires an anthropologic interpretation; it is a datum that has been interwoven with our entire life history. The practitioner, when helping a patient, does not help the body or something called the soul; he attends to a human being. Sometimes he does so with the aid of physicochemical means; in other cases he helps psychotherapeutically, and he does not do so because he is of the opinion that the suffering is either bodily or physical. When giving medication he does not do so with the idea of having solved the riddle of psychosomatic relationships. We know that the endocrine process influences psychic states and vice versa, but we do not know how the inner being produces all these somatic forms and reactions nor are we in a position to tell how the will is operating when we open or close our hands. As Gaupp expressed it once, it has been a general attribute of our thinking ever since the days of Du Bois-Reymond that we shall never understand the essence of the relationship between body and soul. We can study its possibilities and its extent, the practical usefulness of the correlations, and we can try to understand the significance of the endocrine apparatus, but the essential part of the relationship between somatic and psychic processes will always remain an enigma.

We must not persist in trying to solve that age-old problem of the relationship between body and soul. It is not to be found in the autonomic nervous system; the soul is not localized in the diencephalon any more than it is in the brain cortex or in the pituitary gland, as was thought in the days of Descartes.

This Cartesian conception of the duality of body and soul confronts us with a typical

difficulty when studying human behavior which cannot be overcome by means of our science, which has been split into biology and psychology. It is only by a psychosomatic approach that we, working in the center of psychosomatic medicine, can try to gain an understanding of the etiology of human sufferings.

SUMMARY

Our investigations thus far have led us to make the following biologic and pathogenetic observations.

1. Each affect is associated with a certain condition of the autonomic nervous system and the endocrine apparatus.

2. Biologic reaction patterns are intended to serve for a short time and are, as such, harmless.

3. Man can influence the natural psychophysical situation by restraint, suppression, and repression, thus maintaining the specific psychosomatic relationship so that a situation unnatural to biologic life is provoked.

4. The state of illness that may thus arise has a specific origin, in so far as a certain physical constitution and a certain "historic totality," or personal life history, are associated with a specific psychosomatic affliction.

These four fundamental thoughts are applicable hypotheses that, undoubtedly, need further verification.

RESUMEN

Los trabajos de investigación realizados, nos han permitido hacer las observaciones biológicas y patogénicas siguientes: 1. Cada afección está asociada con un cierto trastorno del sistema nervioso autónomo y del aparato endocrino. 2. Se entiende que los tipos de reacción biológica están destinados a actuar por un corto tiempo y son, como tales, inofensivos. 3. El hombre puede influir las situaciones psicofísicas naturales por medio de restricciones, supresiones y represiones, manteniendo así las reacciones psicosomáticas específicas, de tal manera que se provoca una situación anormal para la vida biológica. 4. El estado de enfermedad que puede surgir de esta manera, tiene un origen específico, en el sentido de que una cierta "historia total" o historia de la vida personal, están asociadas con una aflicción psicosomática específica. Estos cuatro pensamientos fundamentales son hipótesis aplicables que, indudablemente, necesitan una comprobación posterior.

RESUME

Nos recherches conduisent aux observations biologiques et pathogénétiques suivantes:

1) Chaque effet est associé à une certaine condition du système nerveux sympathique et à l'appareil endocrin.

2) Les types de réactions biologiques sont censés durer pendant un temps court et sont, par conséquent, sans danger.

3) L'homme peut influencer la situation psycho-physique naturelle par la restriction, la

suppression et la répression, maintenant ainsi un rapport psychosomatique spécifique, qui provoque une situation anormale à la vie biologique.

4) Pour autant qu'une certaine "totalité historique" ou histoire personnelle sont associées à une condition psychosomatique determinée, l'état de maladie qui en résulte a une origine spécifique.

Ces quatre idées fondamentales sont des hypothèses applicables qui demandent un contrôle plus ample.

Dr. Herbert G. Birch Appointed to Editorial Board

We are pleased to announce that Herbert G. Birch, Ph.D., has joined the National Editorial Board of the JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY. Dr. Birch will bring to the Journal a background of wide experience in both clinical and experimental psychology, as well as in research in the neurologic and psychiatric fields. In the past, Dr. Birch has held appointments at Columbia University, the City College of New York, Yenkes Laboratories of Primate Biology and the Jewish Hospital in Brooklyn. In 1952, he was appointed a fellow of the John Simon Guggenheim Memorial Foundation. At the present, Dr. Birch is research associate in the Department of Physical Medicine and Rehabilitation at the New York University–Bellevue Medical Center. In addition, he is continuing his contributions as one of the foremost teachers of clinical and experimental psychology as Associate Professor of Clinical Psychology at the New York Medical College and the Bird S. Coler Hospital and as lecturer in the Psychoanalytic Clinic, Columbia University.

DR. HERBERT G. BIRCH

Dr. Birch's recent papers and presentations have included reports on "The Epidemiology of Mental Health," "Experimental Investigations in Expressive Aphasia," "Comparative Studies of Maternal Behavior," and "Explorations in the Differential Diagnosis of Mental Retardation."

Psychotic Reactions Caused by Cerebral Tumors

Report of Two Craniopharyngiomas

Kristen Austarheim, M.D.

BERGEN, NORWAY

Reports of cerebral tumors as a cause of mental disturbances and psychotic states are numerous, and the subject is discussed in every textbook and handbook of psychiatry, as well as in monographs,[1] theses,[2, 3] and exhaustive surveys.[4] However, the questions raised by this problem are not yet solved completely, and the last word on this subject assuredly has not been spoken. Since craniopharyngiomas with a psychotic reaction as the predominant symptom complex have received little attention, the following cases may be of some interest.

CASE HISTORIES

Case 1. In 1940 an unmarried woman, born in 1906, became depressed and developed religious preoccupations and anxiety. Previously she had exhibited a cheerful, even disposition. The family history indicated that her father was institutionalized in a mental hospital and that her two younger brothers, who had supernumerary fingers and toes, were mentally deficient and had gradually become blind.

The period of depression in 1940 was transitory, but in 1948 the patient became restless and sleepless, was engrossed in persecution conceptions and poisoning notions, and developed hallucinations with influence phenomena. After a course of electroshock in a hospital, she returned to work. However, she continued to complain of her "nerves" and gradually became dull and fussy, with nonsensical and stereotyped ideation. In 1950 she received another course of electroshock treatment, but with less effect. She did not return to work after she was discharged from the hospital, and in October, 1950, two months after discharge, she was admitted to a mental institution, where she remained until her death.

During her stay in the hospital her condition varied. At times her behavior was nonsensical and superficially euphoric; at other times her thinking was rather methodical and coherent. Her vision was greatly reduced, but she had no headaches. Radiographic examination of the cranium and air encephalography suggested the probability of an intracranial tumor. Atrophy of the optic disc of the primary type was found at the final eye examination.

An application was made for her admission to a neurosurgical hospital department, but before she could be admitted she suddenly became much worse, with every sign of an acute rise of intracranial pressure and with failure of respiration and circulation. Death occurred on Dec. 27, 1950, when the patient was 44 years old, and the clinical diagnosis was cerebral tumor.

At a partial postmortem examination a tumor the size of a pullet's egg was found on the base of the brain rostral to the pons, corresponding to the third ventricle. It covered the chiasma, pressed on the optic nerves from the side, and was adherent to the pedunculi cerebri. When these adhesions were loosened, the tumor was found to have a pedunculated attachment to the hypothalamic region, corresponding to the infundibulum. The tumor

From The Institute of Psychiatry, Neevengaarden Mental Hospital, University of Bergen, and The Gade Institute, Department of Pathology, University of Bergen.

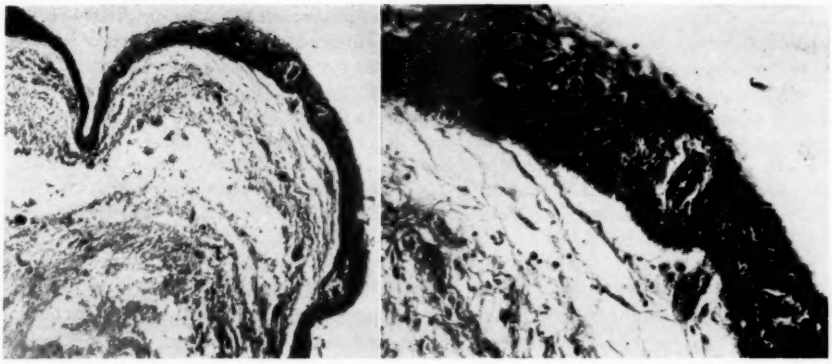


FIG. 1. (left) Photomicrograph (×31 H. & E.) showing the wall of the cyst is composed of multilayered squamous epithelium with a hint of cornification here and there. FIG. 2. (right) Enlarged photomicrograph (×111 H. & E.) of the same structures as in figure 1.

consisted of a single, thin-walled cyst. It did not come into contact with the large vessels on the base of the brain. The left ventricle, the floor of which was as thin as paper, was possibly a trifle dilated. Microscopic examination of the wall of the cyst (Fig. 1 and 2) showed that it was lined internally by pavement epithelium consisting of one or several layers, with here and there a hint of cornification. Under this epithelium there was fibrillary connective tissue that contained numerous blood-filled cavities. Postmortem diagnosis was epidermoid cyst in the region of the hypothalamus, probably starting from Rathke's pouch (craniopharyngioma); however, the alternative diagnosis of an epidermoid (dermoid) tumor with its special mode of origin could not be dismissed with certainty.[5]

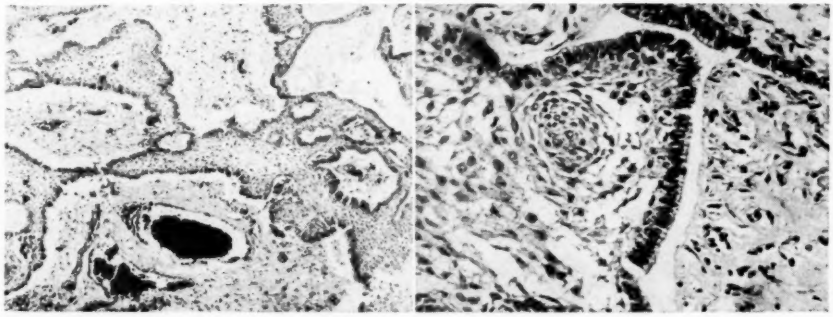


FIG. 3. (left) Photomicrograph (×24 H. & E.) showing ramified, multilayered epithelial tissue with the basal layer consisting of tall, cylindrical, light-colored epithelial cells. The intervening loose connective tissue contains vessels of different sizes. FIG. 4. (right) Enlarged photomicrograph (×86 H. & E.) of the same structures as in figure 3. The basal layer of tall, cylindrical epithelial cells (ameloblasts) are clearly seen.

Case 2. A bachelor, born on Dec. 5, 1882, with no record of mental disease in his family, had suffered a great deal from headaches in his early years. In 1909 he was admitted to an institution because of prolonged drinking which culminated in a delirium-like state. During his stay in the hospital he complained constantly of headaches, and he suffered from both visual and auditory hallucinations. He had paranoid delusions, insisting that the other patients disliked him and influenced him by a Primus-magnetizing apparatus (influence phenomena). He was diagnosed as insane and spent the rest of his life under private nursing care or in an institution. He was silent and quiet at times, restless occasionally, and, on a few occasions, violent. He never spoke to anyone but mumbled and prattled to himself and was unapproachable. Toward the end of his life he was confined to bed and was quite helpless. His vision was greatly reduced. A sudden rise of his temperature on July 29, 1952 ended in his death.

At a postmortem examination a dark, brownish red tumor as large as a moderately sized tomato was found on the base of the brain, extending backward toward the pons. It covered the median parts of the pedunculi cerebri and the whole of the chiasma region. It extended somewhat forward under both frontal lobes, covering some of the olfactory tract. This tumor was polycystic and its dark, blood-stained contents were partially coagulated. It was adherent to the infundibulum and was secured to the chiasma region by vascular and meningeal strands. There was an intimate connection between it and the wall of the third ventricle, which remained with the tumor when it was detached. The tumor had left an impression on the brain substance, particularly on the frontal lobes. Microscopic examination (Fig. 3 and 4) showed a much ramified, papillomatous, multilayered epithelium tissue. The basal layer consisted of very tall, cylindrical cells with light-colored cytoplasm. The epithelial tissue was otherwise composed of polygonal cells, and it presented areas of loose, mucous-like tissue and cysts. There were also small, compact islands of very tightly packed epithelial cells. These islands showed a quite plain spiral structure. At no point were any intercellular bridges found. The connective tissue stroma was scanty, poor in cells, and hyalinized, and here and there calcification was found. Examination of the dura also revealed a soft, slightly pedunculated nodule the size of a pea in the posterior cranial fossa. Microscopic examination showed it to be a meningioma. The right femoral vein was found to be thrombosed, and there were emboli in the right pulmonary artery accounting for the immediate cause of death. Post-mortem examination showed a craniopharyngioma of the adamantinoma or ameloblastoma type.

In the 2 cases described the patients' illnesses were dominated by psychic disturbances primarily involving the emotional sphere in the form of a changed, anxiety-tinged temperament with affective outbreak. Both the intellectual functions and the will power became gradually involved. Dementia set in with apathy, delusions, and hallucinosis. There was diminution of vision amounting almost to blindness. The final stage was characterized by a vacant, lifeless dementia syndrome. A craniopharyngioma was found at autopsy in both cases. It must be admitted that mental disturbances are very common in association with intracranial tumors and are reported in 60 to 100 per cent of the cases on record.[6] As a rule, however, these disturbances develop comparatively late and are of subordinate importance for both symptomatology and diagnosis. It is rare to find patients with tumors whose cases begin with psychic disturbances completely dominating the clinical picture for a long time, or all the time, leading to their hospitalization for mental disease. The psychic

manifestations are determined by the size, character, rate of growth, and localization of the tumor.[7] These manifestations to begin with are often of a more or less psychoneurotic character,[8, 9] and genuine psychoses are said to be exceptional,[3] as the total psyche is reduced to such an extent that the openings for a psychosis are checked. Thus it should be rare to find a more lively symptom output, the psychiatric picture tending to be that of a simple dementia syndrome. The patient suffers from slow cerebration, which rises to torpor animi and ends in coma.[3] However, this applies chiefly to tumors that provoke a rise of the cerebrospinal fluid pressure whereby a more lively development of symptoms is checked. In the absence of such a rise one would expect to find (and one actually does find) a more profuse symptomatology before any drowsy final stage is reached.

There seems to be some uncertainty about how far the position of a tumor affects the character of the patient's mental disturbances. Most authors[4, 7, 9–11] appear to agree that the position of a tumor does play a certain part. Indeed, in certain quarters the possibility has been entertained of the existence of special psychologic syndromes corresponding to the different parts of the brain.[12]

Both the properties of a tumor and the premorbid personality of the patient are of the greatest importance to the pathoplastic evolution of the morbid picture.[3, 6] The mental disturbances often appear as an exaggeration of fundamental personal characteristics or as a regression to earlier modes of reaction.[6] There is a lack of continuity and steady progress of the psychiatric morbid picture particularly when a tumor causes a rise of the intracranial pressure. Occasionally it has an intermittent character running parallel with the rise of intracranial pressure caused by a tumor.[4, 11]

Mental disease may, of course, coincide accidentally with an intracranial tumor, for the incidence of intracranial tumors is much the same in psychiatric patients as it is in other groups of the community. When, however, some causal relationship seemed to exist between a tumor of the cerebrum and some mental disease, it was formerly assumed that the tumor had provoked a latent endogenous psychosis. But, more recent genealogical studies[12, 13] have shown in an apparently convincing way that this is not the case, the pathologic anatomic substratum of the tumor being in itself a sufficient cause.

The special form of tumor found in our cases presents many aspects, and we shall only briefly recapitulate the most important points mentioned in the usual textbooks. Thereafter we will concern ourselves with the psychic disturbances.

Craniopharyngiomas constitute 4 to 5 per cent of all intracranial tumors,[5, 14] being most common in men less than 30 years.[15, 16] The cerebrospinal fluid pressure in 35 to 41 per cent[16, 17] rises, and these tumors may undergo malignant degeneration, invade the surrounding structures, and even give rise to extracranial metastases.[18] They are usually cystic with one or several cavities, and are lined by squamous epithelium, which often shows cornification. It is comparatively rare to find another main type, i.e., an adamantinoma or ameloblastoma. The pathologic anatomy of these tumors are cited in the literature. Erdheim's classic work on the genesis of these tumors[19] has encountered some opposition.[20, 21] The usual symptoms of this type of tumor depend on a combination of a raised intracranial pressure, compression (and possibly infiltration) of the surrounding brain tissue

(with disturbances of vision among others), and changes in the functions of the hypophysis (endocrine dysfunction).[22] On rare occasions, however, the clinical course of a case may take a somewhat unusual turn in the form of psychoneurotic states and massive psychoses. These are the symptoms that are of special interest to the author and his colleagues. Reports of such cases have appeared[23, 24] but they are not common, although they are to be found in the case reports of extensive studies.[3, 15] The point is made that the symptoms appear and reach their peak before any intracranial hypertension has developed.[24]

What are the characteristic features of the psychiatric picture? Let us note that these tumors are close to the diencephalon in which, according to present day opinions, the centers coordinating the emotional life, particularly the more primitive impulses, are to be found. This also explains why it is the emotional sphere that is the first to be involved in these cases, and why the changes are often so far-reaching. Patients who formerly have been quiet and well balanced are apt to become irritable, unstable, obstinate, and difficult, with outbursts of anger and abuse and quite explosive reactions amounting even to aggressive violence. Or the patient becomes quieter and self-centered, presenting a depressive dysphoric picture, often with anxiety states, scruples, and self-reproach. The exact opposite may, however, also be observed, the patient becoming unusually hearty, amiable, elated, and exalted, right up to the pure manic forms.

It will thus be seen that it is the change in the emotional status which first attracts attention. The whole basal character is changed, as is also the psychic rhythm, with blocking and inhibition of the mental processes, an anxiety reaction, or a flight of fancies and confusion of thought with a much increased urge to be active. Other sides of the emotional sphere, such as, warmth of personality, affection, devotion, and a sense of inviolability and consecretion, suffer much and lose their earlier value or significance. And, regardless of whether the basic mentality is at first raised or lowered, the ultimate result is often the same in the form of an indifferent, empty, and dulled emotional life, with the patient oscillating between flat euphoria and toneless apathy.

The direction that the changed basic mentality will take assuredly depends to a great extent on the premorbid personal qualities that make up the fundamental background of the psyche. The mentality makes a selective choice, so to speak, of the mode of reaction. The irritant that the tumor represents is, to begin with, a spur, an incitement to an increased output by the various centers of the brain. Hyperfunction begins, but a persistent irritant, which also constantly increases, leads finally to exhaustion, to a paralysis in the place of the early hyperfunction. It is in this way that we may seek an explanation of the varying, and even contradictory, emotional transitional phases that finally end in a fairly uniform flattened euphoria or an apathic symptom complex that is stationary and irreversible.

Gradually the other psychic functions are also upset. Orientation and sensation suffer, and hallucinosis, which is frequent,[15, 24] is often characterized by very lively and realistic hallucinations. On the whole it would seem that visual, auditory, and olfactory hallucinations are apt to be common in connection with tumors in this position.[25, 26] The ability to comprehend and concentrate attention is diminished, and memory fails, as do the retention

of impressions and the reproductive capacity, with resulting confabulatory states. The faculties of reasoning and imagination are blunted and simplified.

The human psyche is an entity not to be partitioned into separate sectors or zones. As dissolution proceeds, the emotional sphere and intellectual functions become involved, as well as the volitional activities and the drives and needs. Aspontaneity and apathy set in, or the reverse of these qualities appears in the form of a violent motor hyperactivity. The final result is loss of initiative and indolence with a general decline of the energy level.

Disturbances of consciousness also are not rare, and there may be incoherent states, genuine delirium, and Korsakoff-like syndromes. In the end the whole personality, with its sphere of interests and normal standards of behavior, is completely changed, blunted, and reduced. The final stage consists of an empty, lifeless dementia syndrome that merges into sopor and coma terminating in death.

Between 1928 and 1933[27–30] Stertz elaborated his *Zwischenhirn syndrom*, one of the most important contributions to the symptom picture of the morbid diencephalon. Among the many pathologic processes listed in his case records were a few hypophyseal tumors that appeared to be craniopharyngiomas. The comparative uniformity of the syndrome described by Stertz (it coincides with the main points of the picture we have just given) has been challenged by some authors[24] who maintain that such a clear-cut picture cannot be drawn of damages to the diencephalon.

The propinquity of these tumors to the diencephalon also explains why they may be associated with more specific hypothalamic symptoms such as periodic fever, a pathologic sleep rhythm, and hyperpyrexias. The last-named symptom, as well as rupture of the cystic tumor and an acute violent rise of the cerebrospinal fluid pressure (as in 1 of our cases) is the combination of complications that most frequently leads to death.

In the initial phase, before the development of a dementia characterized by dulness and vacuity, the psychic disturbances may be confused with other mental disorders (both psychoneuroses and psychoses including schizophrenia), for hallucinosis is common at this stage. However, with the passage of time, the course of the disease betrays its character, as it sooner or later presents and ends with the symptom-poor dementia syndrome.

As we have already seen, the symptoms presented by our 2 patients on the whole coincided very well with those outlined by Stertz, and with those described in connection with craniopharyngiomas that give rise to purely psychiatric manifestations.

The question then arises as to whether the tumors found in our 2 cases really were responsible for the clinical picture these patients presented. The first patient had a family history of mental disease, but her premorbid personality showed no deviations from the normal. She seemed to have been a harmonious, well-balanced woman; however, it is very difficult to dismiss the possibility that some endogenous psychosis had been in the background and had been stirred into activity by the tumor. In any case there seems to have been a causal relationship between the tumor and the psychosis, but we cannot be perfectly sure to what degree the tumor was responsible for the whole illness or whether a latent endogenous psychosis should figure in our calculations. Yet it seems unreasonable to assume that the association of tumor with mental disease was altogether a mere coincidence. As for

the second patient, nothing in his background suggests mental illness, and it may well be that his headaches, which began when he was quite young, were caused by the tumor. What makes the matter somewhat problematic is the prolonged course of his illness and the clinical manifestations that in many respects were those of schizophrenia. However, this "schizophreniform" phase of his illness disappeared fairly soon, and during most of his life he presented a lifeless dementia syndrome with dulness, vacuity, apathy, and diminution of vision ending in blindness. (These on the whole are the classic symptoms of a craniopharyngioma when the more lively transitional stage has been passed.)

We cannot with certainty dismiss the possibility that an association of an endogenous psychosis (schizophrenia) and a tumor is merely a coincidence in this case. On the other hand, there is nothing to prevent us from holding the tumor responsible for the whole of the patient's illness. Therefore, in this case also we must leave unanswered the question of whether the tumor in itself was the cause or whether it had stirred a latent endogenous psychosis into activity.

SUMMARY

An account is given of 2 patients whose illnesses were dominated by mental disturbances. These at first involved the emotional sphere in particular and then took the form of a change of temperament, with anxiety reactions and affective instability. The intellectual functions, the volitional activities and the drives and needs became gradually involved, and delusions set in with hallucinosis, dementia, and apathy. Vision was reduced almost to blindness. In both cases the final stage was characterized by a lifeless, vacant dementia syndrome. One of the patients was ill for 10 years, the other for fully 40 years. In both cases a craniopharyngioma was found on a post-mortem examination.

The extent to which a causal relationship exists between the clinical picture and the tumor is discussed, as is also the possibility of the association of the two being a mere coincidence. We are convinced that in the first case there was a causal relationship, but we cannot be sure how far the tumor may have evoked a latent endogenous psychosis or whether it was responsible for the whole illness. The second case is more difficult to explain, as the clinical picture was in many respects that of schizophrenia. The long duration of the illness should also be noted. Without being dogmatic on the subject, it seems that in this case also there is nothing to exclude the possibility of a causal relationship of the tumor with the clinical picture.

RESUMEN

En 2 pacientes, cuyas enfermedades estaban dominadas por trastornos mentales, al hacerles la autopsia se les halló un craniofaringioma. Se explica en este trabajo hasta qué punto existe una relación entre el cuadro clínico y el tumor, así como la posibilidad de que la asociación de ambos sea una mera coincidencia.

RESUME

Chez deux malades où la maladie était dominée par des troubles mentaux, l'autopsie

démontra un cranio-pharyngiome. Le degré auquel une relation causale existe entre l'état clinique et la tumeur, et la possibilité que leur rapport soit une simple coïncidence, est discute.

BIBLIOGRAPHY

1. Schuster, P., cited by Rosanoff, A. J.: Manual of Psychiatry and Mental Hygiene, ed. 7, New York, 1947, pp. 488–499.
2. Baruk, H., cited by Marty, R.: Les troubles psychiques dans les neoformationes intracraniennes, Encephale *41*:444–490, 1952.
3. Hermann, K.: Om psykiske funktioner ved intracranielle svulster, Copenhagen, Denmark, 1944.
4. Marty, R.: Les troubles psychiques dans les neoformationes intracraniennes, Encephale *41*:444–490, 1952.
5. Peyton, W. T.; French, L. A., and Baker, A. B.: *In:* Baker, A. B.: Clinical Neurology, New York, 1955, vol. 1, pp. 449–452.
6. Waggoner, R. A., and Bagchi, B. K.: Initial masking of organic brain changes by psychic symptoms, Am. J. Psychiat. *110*:904–910, 1954.
7. Rosanoff, A. J.: Manual of Psychiatry and Mental Hygiene, ed. 7, New York, 1947, pp. 448–499.
8. Nielsen, J. M., and Thompson, G. N.: The Engrammes of Psychiatry, Springfield, Ill., Charles C Thomas, 1947, pp. 385–389.
9. Langfeldt, G.: Laerebok i klinisk psykiatri, Oslo, Norway, 1951, pp. 449–450.
10. Noyes, A. P.: Modern Clinical Psychiatry, ed. 3, Philadelphia and London, 1948, pp. 264–266.
11. Wimmer, A.: Speciel klinisk psykiatri for studerende og laeger, Copenhagen, Denmark, 1936, pp. 122–123.
12. Büel, W. H., cited by Wanner, O.: Genealogische Überprüfung des Wesens der Geistesstörungen bei Hirntumor, Nervenarzt *21*:252–254, 1950.
13. Wanner, O.: Genealogische Überprüfung des Wesens der Geistesstörungen bei Hirntumor, Nervenarzt *21*:252–254, 1950.
14. Grinker, R. R., and Bucy, P. C.: Neurology, ed. 4, Springfield, Ill., Charles C Thomas, 1949, pp. 484–488.
15. Müller, R., and Wohlfart, G.: Cranio-pharyngeomas, Acta med. Scandinav. *138*:121–138, 1950.
16. Haymaker, W., and Anderson, E.: *In:* Baker, A. B.: Clinical Neurology, New York, 1955, vol. 2, p. 1191.
17. Thibaut, F.: Klinik und Histologie der Kraniopharyngeome, Wien. klin. Wchnschr. *59*:409–413, 1947.
18. Kraus, J. E.: Neoplastic diseases of the human hypophysis, Arch. Path. *39*:343–349, 1945.
19. Erdheim, J., cited by Müller, R., and Wohlfart, G.: Cranio-pharyngeomas, Acta med. Scandinav. *138*:121–138, 1950.
20. Tilney, F., cited by Walker, W.: Craniopharyngeoma or para-pituitary adamantinoma (Erdheim's tumour), J. Path. & Bact. *61*:359–366, 1949.
21. Walker, W.: Craniopharyngeoma or para-pituitary adamantinoma (Erdheim's tumour), J. Path. & Bact. *61*:359–366, 1949.
22. Bailey, P.: Intracranial tumors, ed. 2, Springfield, Ill., Charles C Thomas, 1948, pp. 113–137.
23. Wagner, W.: Zur Problem affektiver Veränderungen bei Störungen im Bereich des Zwischenhirns, dargestellt an den klinischen und autoptischen Befunde von drei Craniopharyngeomen. Deutsche Ztschr. f. Nervenh. *154*:1–28, 1942.
24. Riser, Dardenne, Ferdiere, and Gayral: Les formes psychiques precoces des cranio-pharyngiomes, Ann. méd.-psychol. 2:241–254, 1945.
25. Gibbs, F. A., cited by Rosanoff, A. J.: Manual of Psychiatry and Mental Hygiene, ed. 7, New York, 1947, pp. 488–499.
26. Tarachow, S.: The clinical value of hallucinations in localizing brain tumors, Am. J. Psychiat. 97:1434–1442, 1941.
27. Stertz, G., cited by Hermann, K.: Om psykiske funktioner ved intracranielle soulsten, Copenhagen, Denmark, 1944.

28. Stertz, G.: Die Symptomatologie der Tumoren im Bereich des Zwischenhirns (Zwischenhirnsyndrom). Ein Beitrag zur Lokalisation psychischer Störungen, Arch. f. Psychiat. 88:794–797, 1929.
29. Stertz, G.: Über den Anteil des Zwischenhirns an der Symptomgestaltung organischer Erkrankungen des Zentralnervensystems: Ein diagnostisch brauchbares Zwischensyndrom, Deutsche Ztschr. f. Nervenh., 1931, no. 117–119, pp. 630–665.
30. Stertz, G.: Problem des Zwischenhirns, Zentralbl. f. d. ges. Neurol. u. Psychiat. 65:450-451, 1933.

MD Publications to Present Exhibit at Meeting of American College of Physicians

MD Publications, Inc., will be represented with a technical display at the Thirty-eighth Annual Session of the American College of Physicians, which will be held in Boston from April 8 to 12. The 1957 display booth of MD Publications will feature (1) MD, the new medical newsmagazine; (2) the six other journals of MD Publications: Antibiotics & Chemotherapy, Antibiotic Medicine & Clinical Therapy, International Record of Medicine, Quarterly Review of Pediatrics, Journal of Clinical and Experimental Psychopathology & Quarterly Review of Psychiatry and Neurology, and Quarterly Review of Surgery, Obstetrics and Gynecology; and (3) *Antibiotics Annual 1956-1957*, containing 155 reports on the latest findings in antibiotics by 390 authors representing 12 countries.

Other books published recently by MD Publications, Inc., will also be exhibited. These include: the MD International Symposia Monographs—*Health and Travel, Medical Writing, Psychiatry and Religion,* and *Medicine and Writing.*

Glycyrrhiza (Licorice) in the Treatment of Psychiatric Illness

A Preliminary Clinical Report

Werner Simon, M.D., and Robert V. Edwards, M.D.

PSYCHIATRIC SERVICE, VETERANS ADMINISTRATION HOSPITAL, AND THE DEPT. OF PSYCHIATRY
UNIVERSITY OF MINNESOTA MEDICAL SCHOOL, MINNEAPOLIS, MINN.

It is generally hypothesized by psychiatrists of most schools of thought that severe repeated emotional stress leads to psychiatric illness. Selye[1] has demonstrated that emotional reactions such as fear, tension, and frustration cause endocrine imbalance and that these stimuli, when recurrent and sufficiently severe, may produce hypertrophy of the adrenal cortex, ultimately leading through exhaustion to hypoadrenocorticism. Conversely, patients treated with cortisone for medical diseases have been known to show such side reactions as euphoria or depression, or even psychosis. This suggests a relationship between endocrine balance and psychiatric illness. Hoagland et al[2] in a series of studies have investigated the adrenocortical status in schizophrenia and have expressed the opinion that schizophrenic patients show evidence of both hyperadrenalism and hypoadrenalism and that qualitative, rather than quantitative, alterations in adrenocortical function may be of significance. That a favorable response to electroshock therapy is based on a mechanism of release of endogenously produced corticotropin has also been suggested.[3] Psychotic patients who show no adrenocortical response to a test dose of corticotropin also tend to show no improvement after electroshock treatment, as demonstrated by Reiss et al.[4] Other investigators, notably the Sacklers,[5] have postulated a hyperadrenocortical state in schizophrenia, based on their interpretation of laboratory and clinical data.

Working with these concepts, several attempts have been made to utilize replacement therapy in treating psychotic patients. Jens,[6] using desoxycorticosterone acetate, a synthetic steroid, has reported a controlled study of 21 psychotic patients, of whom 3 recovered, 14 improved, and 4 remained unimproved; in her control group of 26 patients, only 2 recovered, 5 improved, and 19 showed no change. Cohn, Karnosh, and Stecher[7] treated 6 patients with severe chronic psychoses, refractory to conventional forms of therapy, with cortisone and observed remarkable improvement in all their patients. They raised the question of whether adrenal refractoriness in the chronic patient, which may cause him to be unresponsive to electroshock, can be altered by a course of cortisone. In a subsequent publication, Cohn, Steckler and Rubinstein[8] reported a controlled study of 21 psychotic patients treated with large doses of cortisone daily for one month and found that 42.8 per cent showed significant improvement. In the field of alcoholism, replacement therapy has been attempted by Lovell and Tintera,[9] who postulate the existence of hypoadrenalism in alcoholics and drug addicts. They selected the term hypoadrenocorticism to indicate "a level of adrenal insufficiency comparable in certain respects to a subclinical Addisonian syndrome." Their use of adrenal cortical extract (ACE) in the treatment of alcoholism

and drug addiction is based on this concept, and the efficacy of their therapy has been duplicated by other clinical investigators.[10]

In searching for other substances with adrenocortical effects which could be used in replacement therapy, our attention was drawn to a substance called *Glycyrrhiza*, an extract of the roots of *Glycyrrhiza glabra*, commonly called licorice. Glycyrrhizinic acid is a polyterpene compound with a structural formula closely resembling the steroid group to which desoxycorticosterone belongs. The extract of licorice has been used for many years to disguise the taste of drugs, as well as in various forms of candy for children.

A survey of the literature reveals that in 1950 Molhuysen and Gerbrandy,[11] at the University of Amsterdam, Holland, reported clinical observations indicating licorice has a pronounced desoxycorticosterone-like action. They made careful electrolyte studies on their patients and found striking individual quantitative differences, apparently due to differences in homeostatic-regulating mechanisms. In 1951 Groen et al[12] observed that a patient with Addison's disease could be maintained in electrolyte balance on extract of licorice. Withdrawal of the extract was followed by reappearance of clinical, biochemical, and hemodynamic disturbances. A second course of *Glycyrrhiza* again produced a clinical remission. In a subsequent publication, Groen et al[13] reported that the crude extract of the roots of *G. glabra*, commonly called licorice, produced sodium and chloride retention and increased potassium excretion in normal individuals and in patients with Addison's disease. They published a case report of a patient with Addison's disease who was maintained daily on 3 to 4 Gm. of ammonium glycyrrhizinate, as shown by electrolyte balance studies. On withdrawal of *Glycyrrhiza* this patient responded with sodium and chloride loss, potassium retention, and clinical signs of dehydration and hemoconcentration. In 1953, Borst et al[14] reported that licorice is not effective unless corticoids are present and postulated that licorice exerts a potentiating effect. Experimenting with animals, Carpetti and Magnani[15] added juice of licorice to the diet of 8 normal guinea pigs for three to four weeks and produced a weight gain of 14 per cent of the initial values, as compared with only 6 per cent in 6 control animals. At autopsy, a 16 per cent decrease in the weight of the adrenal glands was noted, and morphologically the glands resembled adrenals following administration of large doses of desoxycorticosterone in that a functional rest of the glomerular zone was observed.* Hudson et al[16] investigated the in vivo conversion of licorice to biologically active steroid substances by studying 3 patients with advanced cancer who had bilateral total adrenalectomy. They found that administration of *Glycyrrhiza* to patients maintained on oral cortisone acetate did not result in an increase of 17-ketosteroid excretion and that excretion of 17-ketosteroids in patients maintained solely on licorice was negligible. In a more recent publication, Hudson et al[17] was unable to maintain adrenalectomized patients on *Glycyrrhiza* alone; however, he observed that the necessary dose of cortisone was greatly reduced when licorice was added to the treatment regimen. This supports Borst's observation that licorice produces a potentiating effect on exogenous or endogenous corticoids.

In light of the mentioned investigations, the authors[18] selected a patient with meperidine

* This may point to reduced adrenocortical output following administration of licorice.

hydrochloride addiction and treated him with a combination of ACE and *Glycyrrhiza*. The clinical impression gained was a favorable rapid response in withdrawal from narcotic addiction, objective and subjective improvement occurring approximately 13 hours after the first dose of *Glycyrrhiza*. It was felt that *Glycyrrhiza* might exert an influence on the course of other psychiatric illnesses, and a clinical trial with a larger number of patients seemed indicated. The following case reports describe the response of 7 selected psychiatric patients to a trial on *Glycyrrhiza* medication.

CASE REPORTS

Case 1.—A 32 year old single sheet metal worker had a nine year history of stomach distress, diarrhea, constipation, lethargy, migrating pains, urinary frequency, and headaches. His private physician had treated him with repeated prostatic massages. He had received periodic psychotherapy and symptomatic medication for six years without relief. He was always tired, listless, and discouraged. Passive dependency was a prominent characteristic. For a year he was seen every two to four weeks on an outpatient basis in an effort to support him with symptomatic medication, but his condition grew worse. He was then started on daily doses of 2 ml. of fluid extract of *Glycyrrhiza*, and all his symptoms showed dramatic improvement. As the severe diarrhea abated, he became more aggressive and reported feeling better than he had in years. After several weeks of licorice therapy, he ran out of licorice. Two days later he developed malaise and tiredness and went to bed believing he had the "flu," although he stated that it felt unlike any "flu" he had ever experienced. Twenty-four hours later he was improved. The patient was again placed on licorice and for several months has continued to maintain a considerably improved state, although not to such a dramatic degree as during the first few weeks. Surprisingly, he has begun to talk spontaneously of his unsatisfactory interpersonal relationships and to ruminate as to what might be done about them.

Case 2. A 39 year old married watch repairman entered the hospital suffering from a paranoid state of several months' duration. He was certain a fellow workman was putting drugs in his food so as to make him sick and inept at his job in order to replace him. He expressed a desire to have the police called to investigate. In addition, he complained of backaches, lassitude, inability to concentrate and work rapidly, and lack of stamina. These symptoms first began eight years previously following meningitis, which had complicated the removal of a herniated disc. Hospital records indicated a temperature of 104 to 105 F. at that time. Physical examination revealed a blood pressure of 100/90 mm. of mercury, a low pulse pressure, and no positive neurologic findings. In view of the lassitude and hypotension, 2 ml. daily of fluid extract of *Glycyrrhiza* was tried, with the possibility in mind that the patient might be suffering from subclinical Addison's disease. Within a week the patient reported increase in appetite, ability to concentrate, stamina, and ambition. The delusional system decreased considerably in intensity. He was discharged from the hospital after two weeks as improved but was still slightly paranoid. Blood pressure on discharge was 112/78 mm. of mercury. He has had follow-up treatment every one or two months for a year. Six months later there were no detectable delusions. Four times *Glycyrrhiza* was discontinued. Each time he developed weakness, lassitude, inability to concentrate, and decreased work efficiency approximately four to five weeks after stopping therapy. His blood pressure at these times would drop to 100/90 or 110/95 mm. of mercury whereas during his improved periods it ranged from 120/90 to 140/80 mm. of mercury. He reported that he always began to feel well again four to five days after restarting the licorice. The dose of *Glycyrrhiza* was stabilized at 8 ml. of fluid extract every other day. After three months he reported several weak and tired spells. His blood pressure had dropped to 105/95 mm. of mercury, and he was placed on 20 ml. of fluid extract daily, with instructions to reduce this gradually to 10 ml. daily.

Case 3.—A 37 year old married cook suffered for at least eight years with anxiety, irritability, insomnia, fatigue, headaches, nausea, and tremulousness. Over a five year period he had failed to respond to psychotherapy and symptomatic medication. His condition became worse and hospitalization was considered. Physical examination revealed a blood pressure of 100/40 mm. of mercury in the presence of severe anxiety (one and one-half years previously his blood pressure had been 135/90 mm. of mercury). Because of this hypotension,

the patient was placed on syrup of *Glycyrrhiza*, 10 ml. daily. One week later his blood pressure was 130/70 mm. of mercury. The tremor was reduced, his irritability and anxiety were much improved, and his ambition, energy, and stamina were better than they had been in years. For the first time he appeared relaxed. He continued to do well on licorice for several months. However, he reported a distaste for the medication, with gagging and occasional vomiting. Because of this, licorice was discontinued and reserpine substituted. Reserpine was discontinued a few weeks later because the patient became irritable again and argued with his employer; but, after several weeks it was again started, and two months later he was still doing well on it.

Case 4.—A divorced 34 year old assembly worker was an alcoholic for six years. In addition, he suffered for many years with severe stuttering, anxiety, somatic complaints, hypochondriacal fears, and marked passivity. He was admitted to the hospital in a state of apprehension and tremulousness suggestive of impending delirium tremens. ACE was given the first day and then discontinued in favor of syrup of *Glycyrrhiza*, 10 ml. daily. No attempt was made to do psychotherapy; however, the patient spontaneously poured out feelings and information that had never been revealed in previous hospitalizations and extensive outpatient psychotherapy. He told of being hit across the mouth every time he talked back as a child. His stuttering continued. After three weeks he left the hospital, refusing to continue on *Glycyrrhiza* as he did not want to rely on medicine. Five days later he returned, very upset and angry with the therapist but no longer stuttering. He reported that four days after discharge he developed sweats, hot flashes, and a very unpleasant angry irritability. He "told off" his employer, union leader, and girl friend. In addition, he had a heated argument with a stranger and his new landlord. During these episodes his stuttering disappeared but was replaced by numbness of his lips and chin. He was very abusive to the psychiatrist and berated him for not warning the patient what would happen when the licorice was discontinued. He summed up his feelings by stating that he was a lot better off before he took this medicine. However, the patient was given an additional supply of *Glycyrrhiza* with instructions to reduce the dosage gradually. He failed to contact his physician until four months later, at which time he was again anxious, tremulous, and stuttering. He had done well for two months but then resumed heavy drinking. He was placed on 30 ml. of fluid extract of *Glycyrrhiza* daily and told to report in three days. One week later he telephoned his physician. His stuttering was gone, but he was irritable, very demanding, and extremely abusive. When his demands could not be granted, he called the therapist obscene names and hung up. This patient had been known for years as a meek, passive, anxious, and fearful person.

Case 5.—A 37 year old married shoe salesman had suffered for several years with anxiety, obsessive thoughts, a feeling of inferiority, lack of energy, self-abasement, depression, and compulsive behavior. When he tried to call on customers he felt overwhelmed by apathy. He would fall asleep in his car and awaken too late for selling appointments. After several months of unsuccessful psychotherapy, he was given 2.5 ml. of fluid extract of *Glycyrrhiza* daily for four weeks. No detectable change was apparent. Three days after stopping the *Glycyrrhiza* he became severely depressed and lethargic and stayed in bed all day. The next day he awoke refreshed, and full of energy and ambition. He experienced no difficulty in selling and even enjoyed meeting people. The patient reported that he felt better than he could ever remember having felt. His only complaint was heartburn, which he had never had before. He remarked that, because of feeling so well, he had learned a great deal about himself and other people in just a few days. One year later he continues to do well, although his remarkable energy has lessened and his heartburn has disappeared. In the interim he had "told off" his employer, whereas before he had always been completely servile. Psychotherapy was terminated after this apparent rebound phenomenon. The patient is of interest in that his response indicates possible alterations in the emotional state, occurring in time relationship with the electrolyte rebound effect, as demonstrated by Borst.

Case 6.—A 42 year old married man had a history of low back pain, tremors, headaches, and a feeling of weakness in his arms and legs in 1943; subsequently, a disc was removed by surgery. In 1950 he complained of pain in his shoulders, spine, and legs. He also described decreased strength and shakiness that developed on exercise or hard labor. He was impotent, tense and depressed, and cried frequently. In 1954 he complained of pain in the right lumbar region and under the costal margins, belching, tiredness, obesity, headaches, pain in his knees, and lack of ambition. He had not worked in six years, and his wife had become irritated. He had always wanted to be a farmer and had enjoyed gardening. He reported awakening at 3 a.m. and being unable to go back to sleep. Because of previous failure to respond to psychotherapy or symptomatic medication, he

was placed on a daily dose of 2 ml. of fluid extract of *Glycyrrhiza*. Three weeks later he returned very excited and exclaimed that his wife said he was going insane. In explanation he stated that a week after taking licorice he had felt so energetic that he worked in the garden from 3 until 7 a.m., at which time he returned to bed. He was most concerned about losing his appetite and 10 to 15 pounds in weight during this same period. He feared this meant cancer. The patient was given reassurance but failed to maintain further contact.

Case 7.—A 38 year old single car-body repairman sought treatment for tremor of the hands and fingers, vomiting, constipation, and lack of ambition. He was a schizoid person with a long history of chronic alcoholism. He was most disturbed by the vomiting, as it interfered with his drinking. He had been taking sleeping pills, tonics, sedatives, and laxatives. His Minnesota Multiphasic Personality Inventory (MMPI) is shown in figure 1 and indicates a neurotic disturbance with some schizoid trends. The patient was placed on 4 ml. of fluid extract of *Glycyrrhiza*. Four weeks later he returned and reported that he felt better than he had in years. He looked very well and had gained weight. In the interim he had obtained a job and was performing well. He had discarded all his other medication. The MMPI profile taken at this time is shown in figure 2 and reveals a marked drop in the neurotic items, as well as in the schizoid trends. He was given an additional supply of *Glycyrrhiza*. Eight weeks later a third MMPI, which he had been requested to complete, was received in the mail with a letter urgently requesting more medicine. He wrote that he had experienced a sudden return of all of his symptoms three weeks after taking the last dose. His third MMPI, done when he felt ill again, is shown in figure 3, and a rise, especially on the hypochondriasis, hysteria, and schizophrenia scales, is evident. The veteran was sent a supply of *Glycyrrhiza* and has not made contact since then.

DISCUSSION

These clinical trials appear to indicate that *Glycyrrhiza* has potent effects. Since no electrolyte or corticoid studies were attempted, we can only focus on subjective and objective clinical impressions and compare them with those of patients previously presenting complaints and symptoms. It is apparent that, in the majority of the patients described above, symptoms indicative of subclinical Addison's disease, such as weakness, listlessness, lethargy,

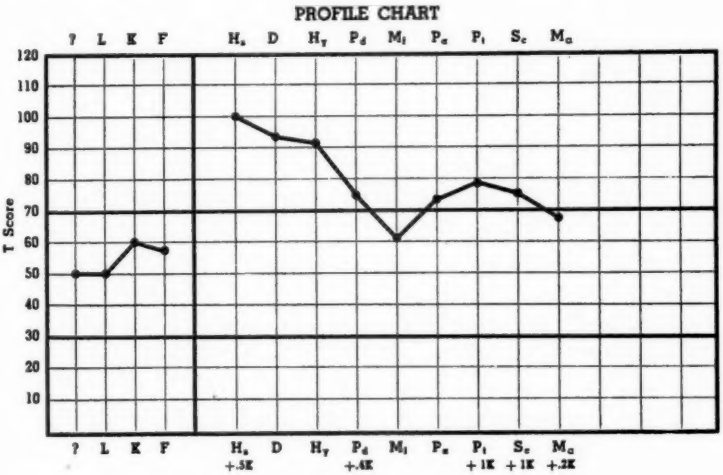


FIG. 1. Patient in Case 7 before *Glycyrrhiza* medication.

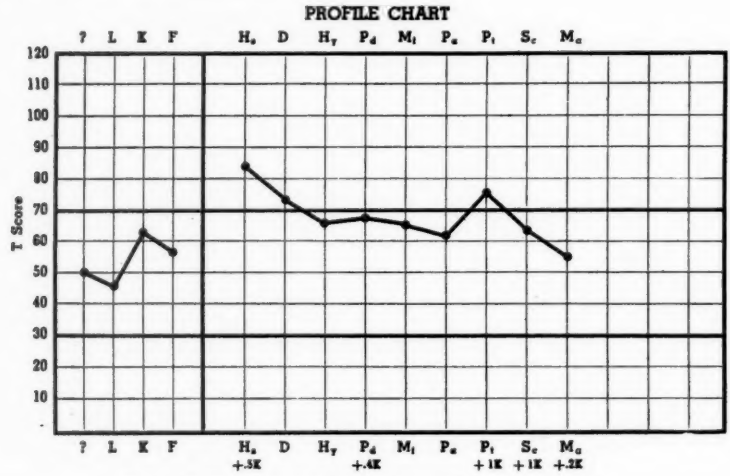


FIG. 2. Same patient after four weeks on *Glycyrrhiza* medication.

and lack of energy and stamina, were changed to a remarkable increase in ambition and energy, coupled with a newly found ability to concentrate and work efficiently. Also, in patients where passivity and dependency are prominent personality characteristics, it becomes evident (in some instances in a rather dramatic fashion) that a change toward aggressive behavior, hitherto unknown in these patients, takes place. The hypotension

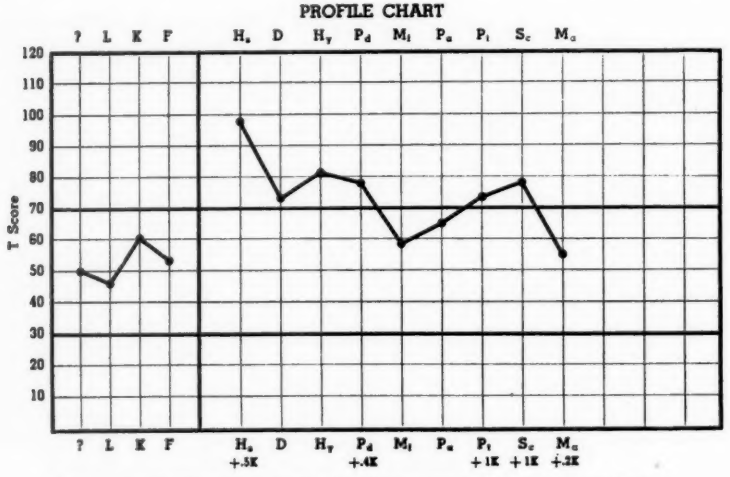


FIG. 3. Same patient three weeks after discontinuance of *Glycyrrhiza* medication.

found in several of our patients, again reminiscent of Addison's disease, was also influenced in some cases and may be a significant factor in appraising indications for this medication, shedding light on physiologic mechanisms. It is possible that blood pressure readings could serve as a guide for dosage and prognosis. The rebound phenomenon, described by Borst, is particularly evident in case 5 where, three days after discontinuing the *Glycyrrhiza* medication, a day of severe lethargy occurred. This was completely overcome the following day when remarkable energy and ambition became manifest. One could interpret this to mean that endogenous corticoids, the production of which had been at relative rest during *Glycyrrhiza* medication, again were produced and circulated. There is reason to believe that, if we are dealing with hypoadrenocorticism due to chronic exhaustion of the adrenals in these psychiatric patients, an imposed rest for the adrenals is made possible through the potentiating effect of *Glycyrrhiza*. This would require a smaller amount of corticoids and therefore less secretory work by the adrenal glands, affording them a relative state of rest. The exact biochemical mechanism of this replacement therapy is as yet unknown, but the resemblance between the chemical structural formula of *Glycyrrhiza* and corticosterones may give rise to speculation concerning the similarity of their physiologic action. However, no increase in 17-ketosteroid excretion has as yet been demonstrated in adrenalectomized patients carried on *Glycyrrhiza* alone. Perhaps future corticoid blood level studies may illume this problem and provide an explanation of the physiologic action of this compound, which apparently has a pronounced, and in some cases even dramatic, clinical effect.

After this clinical trial of a small selected number of psychiatric patients, a larger series, with adequate controls, should be treated with *Glycyrrhiza* to test whether the reported results hold up statistically. It would be desirable to include electrolyte and corticoid studies, as well as daily blood pressure readings, in order to record findings that may be important in explaining the clinical effects of *Glycyrrhiza* thus far observed in psychiatric patients.

SUMMARY

In 7 psychiatric patients treated with *Glycyrrhiza*, symptoms of weakness, listlessness, lethargy, and lack of energy and stamina were beneficially influenced. Passive-dependent personality traits changed into aggressive behavior. In 2 patients hypotension was altered to a normotensive state. That *Glycyrrhiza* has a potentiating effect on adrenal function is hypothesized, and a review of the applicable literature on *Glycyrrhiza*, as well as on replacement therapy in psychiatric illness, is included.

RESUMEN

En 7 pacientes psiquiátricos tratados con Glicirrhiza, se observó una influencia favorable sobre los síntomas de debilidad, falta de atención, letargia y falta de energía y vigor. Los rasgos pasivos y dependientes de la personalidad si tornaron en conducta activa. En 2 pacientes la hipotensión llegó a límites normales. Se sienta la hipótesis de que la Glicirrhiza aumenta la función de la glándula suprarrenal, y se revisa la literatura médica aplicable sobre la Glicirrhiza, y además se incluye como terapia de reemplazo en las enfermedades psiquiátricas.

RESUME

Glycyrrhiza, administré à 7 malades psychiatriques, a grandement influencé leurs symptômes de faiblesse, d'insouciance, de léthargie, et leur manque d'énergie et de vigueur. Les traits de personnalité passive et dépendante ont changé en une conduite agressive. Chez 2 patients, l'hypotension a été changée en un état normotensif. On présente l'hypothèse que Glycyrrhiza aurait un effet puissant sur la fonction surrénale, ainsi qu'une revue de la littérature applicable à l'emploi de Glycyrrhiza, et comme thérapeutique de remplacement dans les maladies mentales.

BIBLIOGRAPHY

1. Selye, H.: Diseases of the Adrenals, Montreal, Canada, University of Montreal Press, 1946.
2. Hoagland, H.; Pincus, G.; Elmadjian, E.; Romanoff, L.; Freeman, H.; Hope, J.; Ballan, J.; Berkeley, A., and Carlo, J.: Study of adrenocortical physiology in normal and schizophrenic men, A.M.A. Arch. Neurol. & Psychiat. *69*:470, 1953.
3. Hoagland, H.; Calloway, E.; Elmadjian, F., and Pincus, G.: Adrenal cortical responsivity of psychotic patients in relation to electroshock treatments, Psychosom. Med. *12*:73, 1950.
4. Reiss, M.; Hemphill, R. E.; Maggs, R., and Haigh, C. P.: Comparative action of E.C.T. and of pituitary anterior lobe hormones on thyroid function, Brit. M. J. *1*:634, 1951.
5. Martí-Ibáñez, F.; Sackler, A. M.; Sackler, M. D., and Sackler, R. R.: The great physiodynamic therapies in psychiatry, J. Clin. & Exper. Psychopath. & Quart. Rev. Psychiat. & Neuro. *17*:1, 1956.
6. Jens, R.: Desoxycorticosterone therapy in certain psychotic cases, A.M.A. Arch. Neurol. & Psychiat. *68*:372, 1952.
7. Cohn, J. B.; Karnosh, L. J., and Stecher, R. M.: Clinical trials with cortisone in the treatment of chronic schizophrenia, Dis. Nerv. System *12*:291, 1951.
8. Cohn, J. B.; Steckler, G. A., and Rubinstein, J.: Effect of cortisone in treatment of psychotic illnesses, J. Clin. & Exper. Psychopath. *14*:161, 1953.
9. Lovell, H. W., and Tintera, J. W.: Hypoadrenocorticism in alcoholism and drug addiction, Geriatrics *6*:1, 1951.
10. Simon, W., and Pearson, R. T.: Adrenal cortex extract therapy in acute alcoholic states, Dis. Nerv. System *12*:311, 1951.
11. Molhuysen, J. A., and Gerbrandy, J.: A licorice extract with desoxycortone-like action, Lancet *2*:381, 1950.
12. Groen, J.; Pelser, H.; Willebrands, A. F., and Kamminga, C. E.: Extract of licorice for the treatment of Addison's disease, New England J. Med. *244*:471, 1951.
13. Groen, J.; Pelser, H.; Frenkel, M.; Kamminga, C. E., and Willebrands, A. F.: Effect of glycyrrhizinic acid on the electrolyte metabolism in Addison's disease, J. Clin. Investigation *31*:87, 1952.
14. Borst, J. G.; deVries, L. A.; Ten Holt, S. P., and Molhuysen, J. A.: Synergistic action of licorice and cortisone in Addison's and Simmond's disease, Lancet *1*:657, 1953.
15. Carpetti, G., and Magnani, B.: Juice of licorice in treatment of ulcer: Experimental and clinical contribution, Gior. di clin. med. *34*:649, 1953.
16. Hudson, P. B.; Mittelman, A., and Mann, P.: Urinary steroid excretion after total adrenalectomy, J. Clin. Endocrinol. & Metab. *13*:1064, 1953.
17. Hudson, P. B.; Mittelman, A., and Podberezec, M.: Use of glycyrrhizin after bilateral adrenalectomy, New England J. Med. *251*:641, 1954.
18. Simon, W., and Edwards, R. V.: The treatment of Demerol addiction with adrenal cortical extract and Glycyrrhiza (licorice): Report of a case, Mil. Med. *117*:43, 1955.

Emotional Aspects of Dermatitis

*Harold Geist, Ph.D.**

BERKELEY, CALIF.

The baffling problems of the etiology and dynamics of skin disease have been studied separately by the dermatologist and psychopathologist in the past half century so as to produce a massive array of specialized literature in this broad area of psychosomatic medicine. Dermatologic ailments themselves often cause a distress of the mind, and, conversely, emotional upsets recently have influenced dermatologists to take note of the possibility of psychologic factors causing, or at least existing concomitantly with, the disorder of the skin.

The concept of psychosomatic medicine goes back to the time of Plato, who said, "For this is the great error of our day . . . that physicians separate the soul from the body." The early literature on the emotional aspects of skin disease emphasized the hysterical and masochistic nature of people affected with dermatologic ailments. The first important application of this approach to dermatology came from Sack[7] of Baden-Baden, Germany, and Mayr, though earlier writers recognized the psychogenic element in specific disorders such as urticaria and pruritus ani. More recently, Ingram[2] asserted that 70 per cent of all cases of dermatitis were of functional origin. Klein,[3] who holds a more radical viewpoint, stated: "Similarly at the risk of being accused of bias, it is felt that there is sufficient evidence to hold the view that every case of dermatitis, until definitely proven to be due to physical or chemical agents, should be recognized as the dermatological manifestation of a deep-seated psychological disturbance." H. Flanders Dunbar,[1] in a comprehensive summary of psychosomatic literature, gave a detailed review of reports on dermatologic manifestations.

This report presents the results of clinical psychologic investigation of patients with five common dermatologic disorders. Subsequent communications will deal with the details of each of the dermatoses and will present illustrative test data from the protocols.

EXPERIMENTAL DESIGN

Fifty patients in five separate diagnostic dermatologic categories, each including 10 patients, were studied by means of the following psychologic tests: the Minnesota Multiphasic Personality Inventory (MMPI), Rorschach, and Draw A Person tests. Test results were analyzed quantitatively and qualitatively in the MMPI and Rorschach, but only qualitatively in the Draw A Person test. The diagnostic categories were made up of patients with acne vulgaris, atopic dermatitis, hand eczema, psoriasis, and cellulitis. The diagnoses were made by the chief dermatologist at the hospital. All patients were male; their ages at the time of administration of the tests were between 20 and 30 years.

MMPI.—The booklet form of the MMPI was administered to each patient. T scores were computed for each of the scales. The mean score for all the patients in this category

* 2900 Telegraph Avenue, Berkeley, California.

for each scale was then computed. For controls, the original standardization group of Hathaway and McKinley at the University of Minnesota Hospital was utilized. These control scales were also plotted on the graph as a method of comparing the scores of the patients with acne and a control group.

Rorschach.—A composite Rorschach psychograph was made by getting the mean of the movement, diffusion vista, texture and achromatic color, and bright color variables of the psychograph.

Draw A Person.—The patients were told to draw a person, then a person of the opposite sex, then the first person undressed, and then the second person undressed. The drawings were analyzed according to the method of Machover.[5]

RESULTS

The data obtained for each diagnostic group are summarized in tables I through V. Table VI presents an over-all summary of all five groups. The most severe psychopathology, as evidenced by the test results, was in the psoriasis group. Differences in T scores on all scales of the MMPI between the psoriasis and the acne group and between the psoriasis and atopic dermatitis group, with confidence levels for each score, are listed in table VII.

TABLE I
Acne Vulgaris

MMPI	Rorschach	Draw A Person	Summary
1. Seven scales with a mean T score of more than 60. Range is from a 49 MF scale to a T score of 67 in schizophrenia and hypomania	1. Lack of color responses	1. Majority of patients drew head only	1. Psychoneurotic with overproductive thought content
2. In the psychotic triad, psychasthenia and schizophrenia scales were high; in the neurotic triad, depression and hysteria scales were high but were lower than the two highest scales of the psychotic triad	2. Introtensive psychograph	2. Profile drawing common	2. Relate poorly to own body image
3. Psychopathic tendencies	3. Schizophrenic responses in several records	3. Signs of sexual disturbance	3. Sexual difficulties
4. Conversion symptoms developed because of dermatologic ailment			4. Schizophrenic diathesis
			5. Tendency to develop conversion symptoms

TABLE II

Atopic Dermatitis

MMPI	Rorschach	Draw A Person	Summary
1. Highest peaks in psychasthenia and hysteria scales	1. Aggressive pattern (FM:M = 3:1)	1. Hostile and paranoid	1. Aggressively hostile and anxious, with disturbance in sexual area
2. Neurotic pattern with obsessive-compulsive element	2. Free floating and intellectualized anxiety	2. Insecurity	2. Fantasy and paranoid tendencies accompanying psychologic impotency
	3. In 50 per cent of cases Card VI rejected		
	4. Fantasy and "distanciation" responses		

TABLE III

Eczema of Hand

MMPI	Rorschach	Draw A Person	Summary
1. Within normal limits except for moderately elevated hysteria scale	1. Relatively "normal" except for rigid personality make-up	1. All figures had hands in pockets	1. Difficulty in sexual area
2. Tendency to develop conversion symptoms			2. Difficulty with authority
			3. Self-conscious of hands
			4. Tendency to develop hysteria conversion symptoms

TABLE IV

Psoriasis

MMPI	Rorschach	Draw A Person	Summary
1. High lie score	1. Anxiety and conflict indicators	1. Rigidly symmetrical figures	1. Marked psychopathology including depression, egocentricity, sensitivity, sexual disturbance, intellectualized anxiety, and obsessive-compulsive characterization
2. High hypochondriasis score	2. Sensitivity, egocentricity, and depression		
	3. Card VI rejected by 3/8 of patients and Card VII by 3/4 of this group		2. Prolific fantasy production and schizophrenic trends

TABLE V
Cellulitis

MMPI	Rorschach	Draw A Person	Summary
1. High lie and Pd score	1. Constricted and rigid pattern	1. Tendency to omit or hide the hands	1. Relative absence of psychopathology except for mild aggression and anxiety and a tendency to fabricate to achieve own ends
	2. Aggression and anxiety		2. Tendency to focus on parts of body afflicted

The major differences are in the lie, hypochondriasis, paranoia, and depression scores. Fabrication appears to be more extensive in patients with psoriasis, and these patients also tend to develop more conversion symptoms concomitant with libido cathexis on their skin ailment. They tend to be less paranoid than patients with acne and atopic dermatitis but more paranoid than patients with hand eczema. They are less depressed than any of the other groups; these patients demonstrate fewer schizophrenic manifestations and are less hypomanic than patients with acne vulgaris. They also show more psychopathic tendencies than those patients with atopic dermatitis.

Hostility.—In a review of the literature, one of the outstanding traits of patients with all skin ailments was hostility. S responses have been mentioned by Rorschach[6] as a measure of "oppositional" tendencies or hostility. Thus the presence or absence of space responses was selected as a quantifiable factor to measure this tendency. Hostility, as measured in this manner, was noted only in patients with psoriasis. The results in all patients were as follows: S (space) was absent in 9 patients with acne vulgaris; in 10 with atopic dermatitis; in 10 with hand eczema; in 4 with psoriasis; and in 10 with cellulitis.

Impulsiveness.—A method of measuring impulsiveness, advocated by Klopfer,[4] is by counting CF responses as compared with FC and at the same time estimating FM:M in the same patients. As Klopfer has stated, "It is easily understandable that a combination of unchecked responses of CF over FC with predominance of FM over M gives the most unfavorable picture (except when found in children below eight years): a mixture of infantilism and lack of control." The results of these determinant ratios appear in table VIII.

Patients in the acne group appear to have the least control, most impulsive behavior, and infantile personalities. It also appears that some patients with psoriasis have this same personality constellation.

Rigidity and Degree of Constriction.—These were measured by calculation of the F per cent for each category. In 10 patients with acne vulgaris, 10 with atopic dermatitis, 10 with eczema of the hand, and 10 with cellulitis, the F per cent was less than 50. It was also less than 50 in 8 patients with psoriasis but equaled 50 in the other 2 patients in that group.

None of the patients in this study were rigid in their personality patterns, as measured by the tests used.

DISCUSSION

Unexpressed rage has been advocated by many of the investigators referred to in this paper as the direct or indirect cause of dermatitis. While this personality disturbance is undoubtedly of major importance, it is entwined with psychosexual deviation, and results of this study seem to point to the area of psychosexual aberration, fixation, or regression. Further research in measuring these aspects of personality is indicated, with quantitative measuring tools constructed for this purpose, e.g., the Blacky Test of Psychosexual Dynamics. Furthermore, the relief form of treatment of these disorders appears to lie in this sexual sphere, with emphasis on dynamic and, in some cases, classical analytic therapy. This does not, of course, exclude organic treatment, but such therapy should be supplemented with, or in some cases replaced by, psychotherapy, depending on the individual case or disorder.

Another significant finding is the high incidence of schizophrenic characteristics in pa-

TABLE VI

Results in All Diagnostic Groups

MMPI	Rorschach	Draw A Person	Summary
1. Hypochondriasis and hysteria scales relatively high	1. Psychograph introtensive 2. Moderate anxiety, (free floating and intellectualized) egocentricity, sensitivity, and depression	1. Insecurity as evidenced by omitting or hiding hands 2. Sexual disturbance 3. Hostility	1. Sexual disturbances 2. Schizophrenic trends 3. Tendency to develop conversion symptoms 4. Overproductive thought content, with tendency to fantasy production

TABLE VII

Psoriasis: Acne Vulgaris

	L	Hs	D	Hy	Pd	Mf	Pa	Pt	Sc	Ma
Difference	2.39	6.54	−7.5	−4.70	−4.64	0.11	−12.98	−1.05	−8.21	−75.0
Confidence level	.025	.0001	.0001	.0001	.0001	.3970	.0001	.2299	.0001	.0001
	L	Hs	D	Hy	Pd	Mf	Paf	Pt	Sc	Ma
Difference	8.06	3.45	−7.22	−.83	8.19	.13	−15.14	−1.19	.69	−1.81
Confidence level	.0001	.0001	.0001	.2789	.0001	.3955	.0001	.1965	.3144	.9735

TABLE V
Cellulitis

MMPI	Rorschach	Draw A Person	Summary
1. High lie and Pd score	1. Constricted and rigid pattern 2. Aggression and anxiety	1. Tendency to omit or hide the hands	1. Relative absence of psychopathology except for mild aggression and anxiety and a tendency to fabricate to achieve own ends 2. Tendency to focus on parts of body afflicted

The major differences are in the lie, hypochondriasis, paranoia, and depression scores. Fabrication appears to be more extensive in patients with psoriasis, and these patients also tend to develop more conversion symptoms concomitant with libido cathexis on their skin ailment. They tend to be less paranoid than patients with acne and atopic dermatitis but more paranoid than patients with hand eczema. They are less depressed than any of the other groups; these patients demonstrate fewer schizophrenic manifestations and are less hypomanic than patients with acne vulgaris. They also show more psychopathic tendencies than those patients with atopic dermatitis.

Hostility.—In a review of the literature, one of the outstanding traits of patients with all skin ailments was hostility. S responses have been mentioned by Rorschach[6] as a measure of "oppositional" tendencies or hostility. Thus the presence or absence of space responses was selected as a quantifiable factor to measure this tendency. Hostility, as measured in this manner, was noted only in patients with psoriasis. The results in all patients were as follows: S (space) was absent in 9 patients with acne vulgaris; in 10 with atopic dermatitis; in 10 with hand eczema; in 4 with psoriasis; and in 10 with cellulitis.

Impulsiveness.—A method of measuring impulsiveness, advocated by Klopfer,[4] is by counting CF responses as compared with FC and at the same time estimating FM:M in the same patients. As Klopfer has stated, "It is easily understandable that a combination of unchecked responses of CF over FC with predominance of FM over M gives the most unfavorable picture (except when found in children below eight years): a mixture of infantilism and lack of control." The results of these determinant ratios appear in table VIII.

Patients in the acne group appear to have the least control, most impulsive behavior, and infantile personalities. It also appears that some patients with psoriasis have this same personality constellation.

Rigidity and Degree of Constriction.—These were measured by calculation of the F per cent for each category. In 10 patients with acne vulgaris, 10 with atopic dermatitis, 10 with eczema of the hand, and 10 with cellulitis, the F per cent was less than 50. It was also less than 50 in 8 patients with psoriasis but equaled 50 in the other 2 patients in that group.

None of the patients in this study were rigid in their personality patterns, as measured by the tests used.

DISCUSSION

Unexpressed rage has been advocated by many of the investigators referred to in this paper as the direct or indirect cause of dermatitis. While this personality disturbance is undoubtedly of major importance, it is entwined with psychosexual deviation, and results of this study seem to point to the area of psychosexual aberration, fixation, or regression. Further research in measuring these aspects of personality is indicated, with quantitative measuring tools constructed for this purpose, e.g., the Blacky Test of Psychosexual Dynamics. Furthermore, the relief form of treatment of these disorders appears to lie in this sexual sphere, with emphasis on dynamic and, in some cases, classical analytic therapy. This does not, of course, exclude organic treatment, but such therapy should be supplemented with, or in some cases replaced by, psychotherapy, depending on the individual case or disorder.

Another significant finding is the high incidence of schizophrenic characteristics in pa-

TABLE VI

Results in All Diagnostic Groups

MMPI	Rorschach	Draw A Person	Summary
1. Hypochondriasis and hysteria scales relatively high	1. Psychograph introtensive 2. Moderate anxiety, (free floating and intellectualized) egocentricity, sensitivity, and depression	1. Insecurity as evidenced by omitting or hiding hands 2. Sexual disturbance 3. Hostility	1. Sexual disturbances 2. Schizophrenic trends 3. Tendency to develop conversion symptoms 4. Overproductive thought content, with tendency to fantasy production

TABLE VII

Psoriasis: Acne Vulgaris

	L	Hs	D	Hy	Pd	Mf	Pa	Pt	Sc	Ma
Difference	2.39	6.54	−7.5	−4.70	−4.64	0.11	−12.98	−1.05	−8.21	−75.0
Confidence level	.025	.0001	.0001	.0001	.0001	.3970	.0001	.2299	.0001	.0001
	L	Hs	D	Hy	Pd	Mf	Paf	Pt	Sc	Ma
Difference	8.06	3.45	−7.22	−.83	8.19	.13	−15.14	−1.19	.69	−1.81
Confidence level	.0001	.0001	.0001	.2789	.0001	.3955	.0001	.1965	.3144	.9735

tients with dermatitis in this study. There is the possibility that dermatologic somatization may be a danger signal of an underlying deeper psychopathology, particularly in the schizophrenic area. It might be well not only for dermatologists but for all people dealing with the dermatoses, especially those dermatoses studied in this paper, to think in terms of underlying psychopathology as an added etiologic agent of the individual disease.

TABLE VIII
Determinant Ratios

	Acne vulgaris	Atopic dermatitis	Eczema of hand	Psoriasis	Cellulitis
CF > FC (with FM more than twice M)	5	–	–	–	–
CF > FC (with FM less than twice M)	–	–	–	2	–
CF = FC	5	6	10	4	10
CF < FC	–	4	–	4	–

CONCLUSIONS

The large problem of the etiology of skin disorders has been reviewed, and an experimental approach to five dermatologic ailments has been presented. Various types of psychopathology have been found in all five diseases in varying degrees. The most severe psychopathology was noted in patients with psoriasis.

ACKNOWLEDGMENTS

The author wishes to thank Dr. Frank Anker for his helpful comments and Dr. Wayne L. Wright for suggesting the project.

RESUMEN

En este trabajo se revisa el amplio problema de la etiología de los trastornos cutáneos' así como un estudio experimental referente a cinco padecimientos dermatológicos. En los cinco casos se hallaron varios tipos de psicopatología en diferentes grados. Los casos psicopatológicos más graves se observaron en el grupo psoriático.

RESUME

Le grand problème de l'étiologie des maladies dermatologiques est analysé et un examen

expérimental de cinq maladies dermatologiques est presenté. Divers genres de psychopathologie furent trouvés, à degrés variables, dans les cinq maladies. La psychopathologie la plus sévère fut trouvé dans le groupe de psoriasis.

BIBLIOGRAPHY

1. Dunbar, H. F.: Emotions and Bodily Changes, ed. 2, New York, Columbia University Press, 1938.
2. Ingram, J. T.: Brit. M. J. 1:187, 1948.
3. Klein, H. S.: Brit. J. M. Psychol. 22:32, 1949.
4. Klopfer, B., and Kelley, D.: The Rorschach Technique, Yonkers-on-the-Hudson, New York, The World Book Co., 1946, p. 85.
5. Machover, K.: Personality Projection in the Drawing of the Human Figure, Springfield, Ill., Charles C Thomas, 1948.
6. Rorschach, H.: Psychodiagnostics, New York, Grune and Stratton, 1942.
7. Sack, W. T.: Psyche und Haut Handbuch der Haut und Geschlechteskrankheiten, Berlin, Juliens Springer, IV, 2, 1302, 1933.

Report from the Menninger Foundation

According to the annual report of The Menninger Foundation for 1955–1956, the enrollment of the Menninger School of Psychiatry is the largest (134 Fellows) since the establishment of the School in 1945. A total of 559 physicians have matriculated in the School. A program has been established in which visiting professors, outstanding leaders in psychiatry and related fields, are to be brought to the Foundation for from several months to a year or two for the benefit of those in training. This program was made possible by a gift of $150,000 from the Sloan Foundation.

Attention has been given to other aspects of professional training, and advanced training in psychiatric hospital administration was instituted during the year. Two physicians are in training under the advanced fellowship program in child psychiatry. The number of students (24) participating in the Foundation's training programs in occupational therapy, music therapy, and recreation therapy is almost double the number enrolled during the previous year. Two Fellows completed two-year programs of postdoctoral training in clinical psychology. The Foundation's first postdoctoral training program in clinical research was completed by three psychologists. In addition, one Fellow has been appointed in child psychology, four in clinical psychology, and one in research.

The Psychotherapy Research Project has now become the major research project of the Menninger Foundation and it involves almost every psychotherapist on the staff. The project was substantially assisted by a grant from the Ford Foundation which totalled $350,000, payable over a five year period. A three year grant was also awarded totalling $60,000 in March 1955 for Research in Psychiatry.

QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

*

Incorporating the International Record of Psychiatry and Neurology

International Editorial Board

INCORPORATING INTERNATIONAL RECORD OF PSYCHIATRY AND NEUROLOGY

FOREWORD

The purpose of the QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY is to present promptly brief abstracts, noncritical in character, of the more significant articles in the periodical medical literature of Europe and the Americas.

For readier reference, the abstracts are classified under the following general headings:

PSYCHIATRY

1. Administrative Psychiatry and Legal Aspects of Psychiatry
2. Alcoholism and Drug Addiction
3. Biochemical, Endocrinologic, and Metabolic Aspects
4. Clinical Psychiatry
5. Geriatrics
6. Heredity, Eugenics, and Constitution
7. Industrial Psychiatry
8. Psychiatry of Childhood
9. Psychiatry and General Medicine
10. Psychiatric Nursing, Social Work, and Mental Hygiene
11. Psychoanalysis
12. Psychologic Methods
13. Psychopathology
14. Treatment
    a. *General Psychiatric Therapy*
    b. *Drug Therapies*
    c. *Psychotherapy*
    d. *The "Shock" Therapies*

NEUROLOGY

1. Clinical Neurology
2. Anatomy and Physiology of the Nervous System
3. Cerebrospinal Fluid
4. Convulsive Disorders
5. Degenerative Diseases of the Nervous System
6. Diseases and Injuries of the Spinal Cord and Peripheral Nerves
7. Electroencephalography
8. Head Injuries
9. Infectious and Toxic Diseases of the Nervous System
10. Intracranial Tumors
11. Neuropathology
12. Neuroradiology
13. Syphilis of the Nervous System
14. Treatment
15. Book Reviews
16. Notes and Announcements

In fields which are developing as rapidly as are psychiatry and neurology, it is obviously impossible to abstract *all* the articles published—nor would that be desirable, since some of them are of very limited interest or ephemeral in character. The Editorial Board endeavors to select those which appear to make a substantial contribution to psychiatric and neurologic knowledge and which promise to be of some general interest to the readers of the REVIEW. Some articles, highly specialized in character, or concerning a subject already dealt with in an abstract, may be referred to by title only at the end of the respective sections.

A section entitled INTERNATIONAL RECORD OF PSYCHIATRY AND NEUROLOGY is included at the beginning of the journal. The Record Section consists of advanced clinical and experimental reports.

The Psychiatry and Neurology Newsletter was compiled by Dr. Francis N. Waldrop.

The Editorial Board at all times welcomes the suggestions and criticisms of the readers of the REVIEW.

WINFRED OVERHOLSER, M.D.
Editor-in-Chief

Psychiatry and Neurology
NEWSLETTER

NIMH PSYCHOPHARMACOLOGY SERVICE CENTER: The National Institute of Mental Health has recently established within its branch dealing with research grants and fellowships a Psychopharmacology Service Center to foster research relating to the "action, efficacy, and limitations of the tranquilizing and other centrally active drugs." Research grants, fellowships, and training grants will be provided through existing programs of the National Institute of Health. The Center will publish a newsletter and summaries of recent and current research and will provide informational, advisory, research, and coordinating services. Interested groups and individuals are invited to contact the Psychopharmacology Service Center, National Institute of Mental Health, Bethesda, Maryland.

GRANTS FOR STUDY OF CEREBRAL PALSY AND MENTAL RETARDATION: The United States Public Health Service has awarded over $700,000 to Yale University School of Medicine and Brown University for a four year study of causes of cerebral palsy and mental retardation. These awards have launched a major research program that is expected to involve at least a dozen institutions and take up to twenty years to complete. The study will also include a search for the factors responsible for disorders such as blindness and deafness.

INTERNATIONAL CONGRESS OF NEUROSURGERY: Brussels will be the site of The First International Congress of Neurosurgery to be held July 21-28, 1957, in conjunction with the International Congress of Neurological Sciences. Registration forms may be obtained from Dr. William B. Scoville, assistant secretary-general, 85 Jefferson Street, Hartford, Connecticut. Neurosurgeons who wish to submit papers to be read at the Congress should send two hundred word abstracts to Dr. Scoville. The American Express Company and Thomas Cook & Son, Inc. will handle hotel and transportation arrangements.

NEW ARNMD OFFICERS: The Association for Research in Nervous and Mental Diseases will hold its 37th Annual Meeting at the Hotel Roosevelt, New York City, December 13 and 14, 1957. The topic will be "The Effect of Pharmacologic Agents on the Nervous System." At the 36th Annual Meeting in New York City, December 7 and 8, 1956, the following officers were elected for 1957: Dr. Francis J.

Braceland, President; Dr. Paul Hoch, First Vice-President; Dr. Carl Pfeiffer, Second Vice-President; Dr. Rollo J. Masselink, Secretary-Treasurer; and Dr. Lawrence C. Kolb, Assistant Secretary.

REPORTING SYSTEM ON EFFECTS OF NEW DRUGS: A pilot system of recording for future reference the reactions of many persons to new drugs is being sponsored by the Food and Drug Administration of the United States Department of Health, Education, and Welfare. Reports are being submitted to a central bureau by eleven leading hospitals, and adverse or unusual reactions to drugs will be carefully noted.

NEW OFFICERS OF AMERICAN ACADEMY FOR CEREBRAL PALSY: The American Academy for Cerebral Palsy held its 10th Annual Meeting in Chicago November 17-19, 1956. The officers for the forthcoming year are: Dr. Nicholas J. Eastman, Baltimore 5, Maryland, President; Dr. William T. Green, Boston, Massachusetts, President-Elect; and Dr. Raymond R. Rembolt, Iowa City, Iowa, Secretary-Treasurer. The 1957 meeting will be held in New Orleans, Louisiana, November 25-27, at the Roosevelt Hotel.

NEW INSTITUTE FOR NEUROPSYCHIATRIC RESEARCH: Establishment of the Arthur P. Noyes Institute for Neuropsychiatric Research at the New Hampshire State Hospital, Concord, New Hampshire, has been announced by Dr. Earl K. Holt, Superintendent, and Dr. G. Donald Niswander, Director of Psychiatric Research and Education. The Institute will be concerned with biochemical and physiological investigation of problems of mental illness. Malcolm Siegel, Ph.D., has been appointed director; he was formerly with the Sloan-Kettering Institute for Cancer Research and the department of biochemistry of Cornell University Medical School.

INFANTILE PARALYSIS FOUNDATION FELLOWSHIP FOR PSYCHIATRISTS: The National Foundation for Infantile Paralysis has announced fellowships of $3600 to $6000 a year for psychiatrists interested in emotional problems of physically disabled persons. Only physicians licensed to practice in the United States and with two years of graduate training acceptable to the American Board of Psychiatry and Neurology are eligible. For further information write the Division of Professional Education, National Foundation of Infantile Paralysis, 120 Broadway, New York 5, New York.

QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

ABSTRACTS

psychiatry

ADMINISTRATIVE PSYCHIATRY AND LEGAL ASPECTS OF PSYCHIATRY

1. *The Clinical Psychologist in the Mental Hospital.* RALPH HETHERINGTON, Dumfries, Scotland. Brit. M. J. 2:708–709, Sept. 22, 1956.

This article describes the work of clinical psychologists at the Crichton Royal, Dumfries, Scotland. The psychologist is based on the ward every day and all day, and he soon becomes a recognized part of the ward team. The patient accepts the psychologist as one of a group that is concerned in his day-to-day treatment. The psychologist is not, then, a stranger called in for a special purpose, but is a well known figure with whom most of the patients talk. When the psychologist works in this way, the value of the material he gains is greatly enhanced. The patient knows him and trusts him, and it is recognized in the ward that patients go to see him. Therefore, there is no strain and no initial discussion before valuable material can be elicited.

Whereas the doctor and the nurses are inevitably in positions of authority, the psychologist is not. He is not required, nor is it necessary, to give orders to anyone. His advice may be sought frequently, but he never assumes authority. This often provides opportunities for the patient to work out his problems when he needs some nonauthoritarian figure to consult. 1 reference.—*Author's abstract.*

2. *Discharge and Readmission Rates in 4254 Consecutive First Admissions of Schizophrenia.* ROBERT H. ISRAEL AND NELSON A. JOHNSON, Warren, Pa. Am. J. Psychiat. *112*:903–909, May, 1956.

All schizophrenics admitted consecutively for the first time (4254 cases) to Warren State Hospital in Warren, Pa., from the year 1913 through 1952 were studied to determine rates of discharge and readmission. Computations of these rates were made according to age and sex. The total cases were classified according to time period of admission, so that the patients admitted in 1913 through 1922, 1923 through 1932, 1933 through 1942, and 1943 through 1952 could be compared in order to learn if prognosis had changed with the years.

This follow-up of each admission discloses true discharge and readmission rates, as contrasted with the usual annual reports that relate discharges during a year only to resident hospital population.

The study revealed that discharge rates of schizophrenics admitted for the first time had never been lower than 54 per cent, even 40 years ago. The rate was fairly constant until the early 1930's when the rate began to rise, first to 61 per cent and later (for the 1943 through 1952 admissions) to 73 per cent. The latter figure is actually lower than the true current picture at the hospital, since it represents the total for a decade of admissions. The current discharge rate for schizophrenic admissions to this hospital is 77 per cent.

The rising discharge rate over the years applied to all age groups; however, since the rate for schizophrenics of less than 20 years had seldom been under 80 per cent, the current discharge rate of 85 per cent seems relatively less of an improvement. For schizophrenics aged 20 to 34 years the discharge rate has risen from 63 per cent to 77 per cent, also a less spectacular increase. Patients aged 35 to 49 years have seen their discharge rate rise from 40 per cent to 73 per cent, while those aged 50 or more, have had the relatively most sensational improvement, their discharge rate being doubled, to a current rate of 50 per cent, as contrasted with the 25 per cent rate of 40 years ago.

Up to 1933, male schizophrenics always had a higher discharge rate than female schizophrenics, but the situation is now reversed, with women having a slightly higher discharge rate than men.

Readmission rates have not increased over the years. A figure of 25 to 30 per cent represented the readmissions for permanent care. Patients currently discharged have a first year readmission rate slightly lower than that of discharged patients of former decades.

This type of historical study gives a clearer and more accurate picture of prognosis in schizophrenia than the usual resident population analyses. The picture is much more optimistic than the latter type of presentation. Improved prognosis during the past 40 years suggests definite value to the new therapies developed for schizophrenia. 10 tables. —*Author's abstract.*

ALCOHOLISM AND DRUG ADDICTION

3. *The Nature and Significance of Brain Damage from Alcoholism.* FREDERICK LEMERE, Seattle, Washington. Am. J. Psychiat. *113*:361–362, Oct., 1956.

It has been known for some time that prolonged heavy drinking can cause permanent damage to the brain. In advanced stages this is manifested clinically by deterioration of the personality; at autopsy it is manifested by gross atrophy of the cerebral cortex.

Although there is no question that repeated excessive drinking can and often does produce permanent brain damage, the extent of such damage is unknown. When one considers, however, that cerebral cortical atrophy is the end product of gradual insidious dissolution of large numbers of brain cells, the conclusion is inescapable that for each alcoholic person with demonstrable damage there must be thousands in the intermediate stages.

In addition to the direct effect of alcohol on the brain are other closely related factors that produce damage to the brain. Among these are anoxia from the cerebral vascular congestion produced by alcohol, repeated head injuries, the obscure but probable toxic effects of cir-

rhosis of the liver, and the malnutrition that so often accompanies heavy drinking. Vitamin B deficiency is especially noteworthy in this respect.

Brain damage is responsible, in many cases, for the permanent loss of control over alcohol that is pathognomonic of alcoholism. In most alcoholic persons brain damage is manifested only by such loss of control. If the alcoholic person stops drinking before too much damage has been done, he will still be able to function normally as long as alcohol is assiduously avoided.

4. *Experiences with Reserpine in the Treatment of Alcoholism.* NATHANIEL S. RITTER, New York, N. Y. Quart. J. Stud. on Alcohol *17*:195–197, June, 1956.

Reserpine was given to 91 alcoholic patients in order to determine its effects on their drinking behavior over a period of time and on their psychologic mechanisms. There were 89 control patients who received a placebo. All patients were seen once a week and were asked how they felt and what their drinking habits had been during the preceding week. Dosage of reserpine was four 0.25 mg. tablets daily. Evaluation was made only in patients who attended the clinic eight weeks or more, namely, in 39 reserpine-treated patients and in 36 controls.

There was "no substantial difference between reserpine and placebo in diminishing drinking."

It is the author's impression "that the very fact that the patient is seen weekly and some personalized interest taken in his condition, plus the administration of some form of oral therapy—be it vitamins, a placebo, or reserpine—helps patients to cut down considerably on their drinking." The only side effect of reserpine in this study was occasional drowsiness. 4 tables.—*Author's abstract.*

BIOCHEMICAL, ENDOCRINOLOGIC, AND METABOLIC ASPECTS

5. *Some Aspects of Suprarenal Function in Schizophrenia (Algunos Aspectos de la Función Suprarrenal en la Esquizofrenia).* LUIS YRURITA. Rev. neuro-psiquiat. *19*:124–131, March, 1956.

Urinary excretion of 17-hydroxycorticoids showed a marked difference between improved and nonimproved schizophrenic patients after they had received adequate treatment. The values of 17-hydroxycorticoids found in unimproved patients are interpreted as the expression of one of the multiple hormonal changes related to mental disorder. There was no statistically significant difference in the groups studied. Endocrinologic research studies should be continued in patients with mental disturbances, bearing in mind the possibility of hormonal treatment.

6. *Lysergic Acid Diethylamide in Patients with Excess Serotonin.* ALBERT SJOERDSMA, CONAN KORNETSKY, AND EDWARD V. EVARTS, Bethesda, Md. A. M. A. Arch. Neurol. & Psychiat. *75*:488–492, May, 1956.

Lysergic acid diethylamide (LSD), a potent hallucinogenic agent, is known to antagonize certain effects of serotonin (5-hydroxytryptamine) on smooth muscle. The notion has been

expressed that the psychologic effects of LSD might be due to an antagonism of serotonin in the brain. The availability of patients with elevated blood serotonin levels seemed to offer an opportunity to test this hypothesis. The patients exhibited the syndrome associated with secreting metastatic carcinoid tumors. LSD, in a dosage of 20 to 80 μg., was given orally to 2 patients, and the psychologic and physiologic effects were observed. The psychologic changes were of an order observed in normal subjects receiving LSD. Aggravation of flushing reactions and bronchospasm following LSD is the reverse of what would be expected to happen following the administration of a serotonin antagonist to a patient with excess serotonin. More direct evidence must be produced to establish a relationship between the central effects of LSD and serotonin in the brain. 22 references. 1 table.—*Author's abstract.*

CLINICAL PSYCHIATRY

7. *Malingering: "Diagnosis" or Social Condemnation? Analysis of the Meaning of "Diagnosis" in the Light of Some Interrelations of Social Structure, Value Judgment, and the Physician's Role.* THOMAS S. SZASZ, Syracuse, New York. A. M. A. Arch. Neurol. & Psychiat. *76*:432–443, Oct., 1956.

Malingering is considered in every textbook on psychiatry and in psychoanalytic writings, as if it were a scientific concept designating a distinct mode of behavior or a psychopathologic syndrome. Observations in settings in which the diagnosis of malingering is sometimes made, together with study and reflection on this subject, lead to the conclusion that the afore-mentioned concept of malingering is unsound from the point of view of both semantics and psychiatric theory. This essay presented an analysis of the concept of malingering, not as an alleged syndrome but as a scientific abstraction.

The exposition of this theme is divided into three parts, based on three more or less distinct frames of reference from which malingering may be viewed. The author distinguishes malingering as a diagnosis, a violation of a set of social rules, such as cheating in games, and a psychopathologic syndrome characterized by special psychologic features. An analysis of malingering in terms of each of these three points is presented. Particular attention is focused on an attempt to clarify, partly in terms of social structure, the meanings of diagnosis.

The principal conclusions of this study can be briefly summarized. 1. Malingering is not a diagnosis in the usual sense of the word and must be eliminated from psychiatric and medical writing as an item in the differential diagnosis of certain diseases. 2. Malingering expresses the physician's moral condemnation of the patient in general and of a specific pattern of behavior in particular. Thus it tells us more about the observer (physician), that is, his identification with the prevailing values of the social group in which he works, than it does about the observed (patient). 3. No rational meaning can be given to malingering as an alleged psychopathologic syndrome. It is suggested that malingering is best viewed in the sociopsychology of games. Accordingly, this notion pertains to social situations in which the physician is a representative of some social body and plays a role analogous to that of an umpire in a competitive sport. It is his duty to see that no one cheats. The malingerer is one who cheats in a game that is a segment of real life. 28 references.—*Author's abstract.*

8. *Stress and Psychiatry.* HANS SELYE, Montreal, Quebec, Canada. Am. J. Psychiat. *113*:423–427, Nov., 1956.

After a brief enumeration of key references to the literature on stress in psychiatry, the following specific problems are discussed on the basis of personal experiments: (1) an operational definition of stress, based on measurable indicators of this state; (2) steroid anesthesia; (3) anticonvulsive and tranquilizing effect of steroids; (4) corticoids and muscular paralysis; (5) morphologic changes in the brain produced by corticoids; (6) stress and inflammatory diseases; and (7) stress and sexual derangements. 15 references.—*Author's abstract.*

9. *A Prisoner of War Syndrome: Apathy as a Reaction to Severe Stress.* HARVEY D. STRASSMAN, Los Angeles, Calif., MARGARET B. THALER, AND EDGAR H. SCHEIN, Washington, D. C. Am. J. Psychiat. *112*:998–1003, June, 1956.

One of the common psychologic reactions to the severe stresses endured by American soldiers captured during the Korean War was the utilization of a psychologic defense that served to maintain personality integration and life. This defense, called apathy, consisted of a paucity of emotion, withdrawal into fantasy and thoughts, and loss of interpersonal relationships. Gradations of apathy, from the mild form to that causing death, were almost universal among prisoners during acute stress.

An unselected group of repatriated prisoners were interviewed psychiatrically, and a second unselected group were tested psychologically at Inchon, Korea, and en route home by ship in August, 1953. The groups were representative of the total group repatriated. It was found that a statistically significant number of men demonstrated apathy clinically and an even greater number demonstrated apathy when tested.

The factors prevalent in the production of the apathy reaction appeared to be the continual frustration of personal goals, disappointment when promises of good treatment by the captors led to more harsh treatment, starvation induced by the captors, disease that was not adequately medically treated, guilt about unwilling participation when indoctrination of communist thought and ideology was attempted, and loss of ties to home and country. When the combination of factors became oppressive, severe apathy appeared to develop to the point where the men chose death rather than fighting to live. Trained medical observers who were themselves prisoners have described no psychiatric or medical illness.

Factors that prolonged the apathy reaction beyond the period of acute stress and for some time after repatriation appeared to be the sustained inability to cope with aggression because of feared retaliation and the fear that control might be totally lost if repressed aggression was allowed to come to consciousness.

The sudden change from prisoner of war to American soldier to civilian was another difficult emotional adjustment. The men, therefore, clung to the prisoner style of adjustment until they felt emotionally safe in making the change. 16 references. 1 table.—*Author's abstract.*

10. *The Responsibility of the Graduate Educator in Neurology and Psychiatry.* BENJAMIN BOSHES, Chicago, Ill. J. A. M. A. *161*:1213–1219, July 28, 1956.

World War II brought about acceptance of the relationship between emotional disturb-

ances and such organic dysfunctions as peptic ulcer, migraine, hypertension, and asthma. Nevertheless, the tendency toward compartmentalization, splitting neurology from psychiatry and even making distinctions between office psychiatry and the handling of acutely disturbed patients, continued to inordinate extremes. The result has been an excessive devotion to particular methods of diagnosis or modes of therapy on the part of the teachers and a commensurate unwillingness to acquire a truly broad training on the part of the students. The deviations and excessive specialization of the trainees out in practice result from similar tendencies among the teachers. Broadness is the essence, for the generation now coming into being must not hand on a tradition of constricted interests and unbalanced perspectives to the generations that follow. 9 references.—*Author's abstract.*

For Reference

11. *Emil Kraepelin: February 15, 1856—October 7, 1926—February 15, 1956.* EUGEN KAHN, Houston, Texas. Am. J. Psychiat. *113*:289–294, Oct., 1956.

GERIATRICS

12. *A Study of Performance in Relation to Age at Two Printing Works.* HILARY M. CLAY, Cambridge, England. J. Gerontol. *11*:417–424, Oct., 1956.

For three years following the introduction of incentive schemes at two printing works, individual production records of hand compositors, machine compositors, and readers, were examined to determine (1) whether or not there was any evidence of a change of performance with age in these high-grade skills, and (2) the effects, if any, an incentive scheme would have on the older craftsmen. Decline of performance with increasing age was small, but it was observed in persons from approximately 50 years of age and up among the compositors. The older readers maintained their output at a higher level than did the younger ones. At both printing works, no relationship was observed between age and the general increase in output following introduction of the incentive schemes. The older skilled craftsman who has been working well within his capacity may improve or at least maintain the rate of work under incentive conditions. 11 references. 4 tables.—*Author's abstract.*

13. *Aged in Connecticut State Mental Hospitals.* SIDNEY SHINDELL AND ELIZABETH CORNFIELD, Rocky Hill, Conn. J.A.M.A. *160*:1121–1125, March 31, 1956.

Crowding in mental hospitals has at times been ascribed to a supposedly large number of senile patients who do not really need the facilities of psychiatric care and could be transferred to other institutions for the aged or chronically ill. A representative sample from each of the three state hospitals in Connecticut was studied to determine the extent to which care outside a mental hospital was feasible for these elderly patients.

Of a total of 10,289 patients, 40.6 per cent were aged 60 years and older. A 10 per cent random sample of the latter group (417) was obtained. Diagnoses showed that the majority of the older persons residing in the mental hospitals could not be considered simply problems of senility or of circulatory disease of the brain accompanying older age, since only 36 per cent of the group were found to be in these categories. Also, a large number of older patients in the mental hospitals have grown older there. Less than half (47.2 per cent) were 60 years

or older when last admitted. Only 36.7 per cent of the survey group were 65 or older on admission. In determining which patients could be transferred to a chronic illness hospital, the criteria used were that manifestations of illness constituted no danger either to the patient or to the other patients and that the patient's behavior could not be so sociably unacceptable or disturbing as to interfere with adequate care for other patients. In this way the suicidal, the negativistic, the destructive, the assaultive, and the disoriented were not considered eligible for transfer. In no case was physical illness a factor in disqualifying a patient for transfer. The committee found 291 of the 417 patients not suitable for transfer, leaving 126 (30.2 per cent) of the sample acceptable. Of this latter group, 42 were judged unsuitable for transfer by the mental hospital staff, 3 patients' families refused permission for transfer, 35 had outside arrangements already made, and 5 patients died or were discharged, leaving 46 patients available for transfer.

On the basis of this survey it is seen that the number of aged in mental hospitals who can be cared for elsewhere is a small percentage of the total population of the mental hospital (6.5 per cent), of which more than half (3.5 per cent) have been already removed, though still carried on the hospital census. The number of aged, loosely termed "seniles," who may be cared for elsewhere is only 1.5 per cent of the total mental hospital population. Use of chronic care facilities for aged persons who have been admitted to mental hospitals represents simply one method of care for persons who are in the normal discharge channels of the hospital system. 4 references. 1 figure. 8 tables.—*Author's abstract.*

14. *Memory and Movement; a Study of Their Abnormality in Senile Dementia (Mémoire et mouvement; Étude de leur perturbation dans la Démence sénile).* F. MOREL AND J. J. BURGERMEISTER, Geneva, Switzerland. Monatschr. f. Psychiat. u. Neurol. *130*:359–374, Nov., 1955.

In 9 patients with uncomplicated senile dementia as compared with normal controls, it was found that the ocular movements in looking at a figure that was new to them and in following its outline showed definite abnormalities in these patients as compared with the controls. The memory of these patients in regard to the figure was also faulty. 4 figures. 4 references.

15. *Rauwolfia Tranquilization for the Disturbed Aged.* I. W. RUSKIN AND MILTON AVOL, Los Angeles, Calif. J. Am. Geriat. Soc. *4*:998–1003, Oct., 1956.

The authors report on a psychiatric regimen at the Jewish Home for the Aged in Los Angeles in which two Rauwolfia serpentina preparations were tried as ataractics. Nineteen residents were selected for therapy by the psychiatric staff because they exhibited one or a combination of such symptoms as agitation, depression, confusion, delusions, hallucinations, and generally disturbed behavior.

The rauwolfia preparations used were reserpine and the alseroxylon fraction. There was considerable variation in individual responses to these drugs, and the optimal dosages for different patients varied greatly. Once a salutary effect on the emotional state was obtained, however, average maintenance dosages could be established. A level of 0.5 to 1.0 mg. daily was usually satisfactory for reserpine and 8 mg. daily for the alseroxylon fraction.

Although the series of cases reported is small, the results demonstrate the value of rauwolfia for tranquilization of the emotionally disturbed elderly patient. It appears, moreover, that there was little difference in the effectiveness of the two drugs; patients showing satisfactory improvement with reserpine maintained this improvement when the therapy was changed to the alseroxylon fraction. If no improvement was induced with reserpine therapy, the alseroxylon fraction also had little effect. Data further demonstrated that these are relatively harmless drugs and deserve a place in the armamentarium of geriatric medicine. 5 references. 1 table.—*Author's abstract.*

INDUSTRIAL PSYCHIATRY

16. *A Treatment Program for the Alcoholic in Industry.* ARNOLD Z. PFEFFER, DANIEL J. FELDMAN, CHARLOTTE FEIBEL, JOHN A. FRANK, MARILYN COHEN, STANLEY BERGER, M. FREILE FLEETWOOD, AND SIDNEY S. GREENBERG, New York, N. Y. J.A.M.A. *161*: 827–836, June 30, 1956.

This paper presents a panoramic report on the Consultation Clinic for Alcoholism, University Hospital, New York University–Bellevue Medical Center, with emphasis on administrative policies and procedures, and a discussion of preliminary clinical data obtained from the various treatments of the alcoholic in industry over the past four years. More specific areas reported include the administrative arrangements, referral processes, diagnostic and treatment procedures, preliminary results and impressions of special features of the problem drinker, and implications of the use of probation.

The personnel of the clinic consists of psychiatrists, psychologists, and an internist. Each member receives a stipend and devotes a fixed amount of time to the clinic. Fourteen companies had utilized the services of the clinic by paying a consultation fee for the initial evaluation of their employees. Treatment offered to the employee after this evaluation period is charged on a regular fee basis. Evaluation of the patient's problems and determination of the treatment program are based upon information obtained during initial interviews and from medical examinations, psychological tests, and laboratory studies. Treatment consists mainly of individual psychotherapy of either the directive-supportive or analytic type, group psychotherapy of either type, administration of disulfiram, and other medical procedures.

Data have been obtained covering the treatment program at the Consultation Clinic from February 1952 to April 1955. Specific material is presented dealing with a number of referrals, patients who refused treatment, patients considered untreatable at the Consultation Clinic and referred elsewhere, and hospitalized patients; consideration is given to the age of the patient, the length of time at the clinic, psychotherapy assignments, termination of treatment by patients, and administration of disulfiram. Special attention is directed to data dealing with the absenteeism and maintenance of jobs by the patients. The improvement noted in average days lost per year was from 15 days for the year prior to reporting to the clinic for five days for each year subsequent to reporting for treatment. The frequency of absences per person per year improved from 2.2 for the year preceding study at the clinic to 0.9 after one year of treatment, 1.0 after two years, and 0.6 after three years. In terms of all employees referred to the clinic, 75 per cent have been able to maintain their

jobs. Considering only those referred employees who undertook clinic treatment, this figure is raised to 82 per cent.

The figures obtained in assessing absenteeism and maintenance of jobs is high, and an attempt is made to explain this in a discussion of the special personality features of the alcoholic in industry and in the role of probation in motivation for treatment. 6 references. 4 tables.—*Author's abstract.*

PSYCHIATRY OF CHILDHOOD

17. *The Widening Etiology of Mental Defect.* R. GIBSON, Portage la Prairie, Manitoba, Canada. Canad. M. A. J. *75*:685–690, Oct. 15, 1956.

Depending on the presence or absence of obvious pathologic features, it is possible to distinguish a group of defectives in which cultural, sociologic, or psychologic factors are outstanding, and another group in which mental defect is associated with obvious physical disease or abnormality. The dichotomy originally proposed by Lewis is considered still applicable. Bearing in mind that such groups are by no means mutually exclusive, and with due regard to the ephemeral nature of classifications in this field, a division is made into sociologic and pathologic categories. The former category includes Lewis' subcultural type, exogenous defects as delineated by Strauss, and a small psychopathic or delinquent group.

The pathologic section is an attempt to bring up to date an earlier survey published in 1951. Under this heading are listed conditions in which mental defect accompanies anomalies of the skeletal, neuromuscular, special sense, and cutaneous systems, with mongolism and congenital syphilis treated separately. The skeletal section is further subdivided into cranial anomalies of size, shape, or consistence (that is, hyperostosis frontalis interna), peripheral anomalies, and dwarfism of endocrine, metabolic, or chondrodystrophic type. The neuromuscular section includes conditions characterized by paralyses of diplegic, hemiplegic, or progressive type, striatal disorders, convulsive syndromes, and diseases like dystrophia myotonica. Anomalies of special sense organs include ocular conditions in the presence of gross abnormalities, such as optic atrophy or retinopathy, as well as aural and olfactory conditions. Cutaneous disorders include ectodermal dysplasia, neuroectodemal dysplasia and pigmentary anomalies.

Among conditions more recently associated with mental defect are von Gierke's disease, the severe form of idiopathic hypercalcemia, familial dysautonomia, idiopathic spontaneous hypoglycemia, pseudohypoparathyroidism, galactosemia, and familial idiopathic hemoglobinemia. Reference is finally made to pseudofeeblemindedness and the confusing use of the term as synonymous with either delayed maturation alone, or with the entire differential diagnosis of mental defect. 31 references.—*Author's abstract.*

18. *Estimating Developmental Potential of Pre-School Children with Brain Lesions.* ELSE HAEUSSERMANN, Brooklyn, N. Y. Am. J. Ment. Deficiency *61*:170–180, July, 1956.

This article describes children who have lesions of the brain with and without motor handicaps. The aim, method, and underlying principle of using a structured interview, with parallel objective and subjective evaluation and conclusion, is described. Reporting on the second phase of a long-term study of testing preschool children with cerebral palsy, the

author is concerned with the deviations in mental, emotional, sensory, and sensory-motor functioning of children with brain lesions. Some illustrations of the approaches and materials used to study the developmental potential of children with brain lesions are given. The evaluation results in a description of total functioning and of the intactness or non-intactness of specific, significant areas of functioning.—*Author's abstract.*

19. *The Concept of Pseudofeeblemindedness.* ARTHUR L. BENTON, Iowa City, Iowa. A. M. A. Arch. Neurol. & Psychiat. *75*:379–388, April, 1956.

The authors point out that the term, pseudofeeblemindedness, has been used in two respects, which are in essence mutually exclusive and which require explicit differentiation. In one usage it represents a mistaken diagnosis, that is, from the data at hand, a child is judged to be mentally retarded or deficient when in fact he is not. Since errors in diagnosis should not be given the status of a clinical entity, it is difficult to justify this usage, and it is suggested that it be abandoned. In the second usage of the term, pseudofeeblemindedness represents mental deficiency of atypical etiology. This atypical etiology may be classified into a number of broad types of determinants, namely, sensory deprivation, motor deficiency, cultural deprivation, and emotional disturbance. A conceptual schema illustrating how these determinants might interact with a person's basic hereditary endowment to produce a condition of behavioral deficiency is presented.

In order to understand the meaning of pseudofeeblemindedness and assess its place in clinical thinking, it is necessary to review true mental deficiency. Analysis indicates that it is a complex concept that possesses behavioral, etiologic, developmental, and prognostic implications. When attention is focussed on high-grade deficiency, one finds considerable disagreement concerning these implications, particularly with respect to etiology and prognosis. Although defect or disease of critical cerebral areas is usually considered at least the proximate cause of true mental deficiency, neuropathologic study has failed to provide convincing evidence of such a basis for high-grade deficiency. Similarly, while a poor prognosis is often considered to be implicit in the diagnosis of true mental deficiency, follow-up studies of high-grade defectives indicate that a significant proportion of persons who were diagnosed in childhood as mentally defective, prove to be socially competent when they reach maturity.

These considerations lead to an attenuation of any fundamental distinction between true mental deficiency and pseudofeeblemindedness. They suggest that traditional concepts of mental deficiency, to the degree that they include specific causes and a neuropathologic basis or course as defining terms, should be abandoned. A broader formulation, which calls for a re-examination of the relations between mental deficiency and mental illness and which reopens the question of etiology, appears to be more adequate. Since we deal with symptom pictures of multiple causes, no one specific cause has any claim to precedence over any other as being the primary antecedent condition of true mental deficiency. On the basis of behavioral criteria, all cases are examples of true mental deficiency. Conditions of pseudofeeblemindedness can be conceived as being true defect states with certain types of etiologic background. Because of their clinical importance, detailed study of the pathogenesis of these conditions is strongly indicated. 12 references. 1 figure.—*Author's abstract.*

PSYCHIATRY AND GENERAL MEDICINE

20. *Relationship of Psychosis and Psychosomatic Disease.* ALEXANDER THOMAS, MARVIN STERN, AND ALFRED LILIENFELD, New York, N. Y. J. Nerv. & Ment. Dis. *123*:249–256, March, 1956.

This article examines the concept expressed frequently in the psychiatric literature that an inverse relationship exists between psychosis and psychosomatic disease. The formulation has led to hesitancy in the treatment of psychosomatic disorders by organic methods that could produce rapid improvement or cure for fear these methods would precipitate psychosis. On the theoretic side, this concept that psychosis and psychosomatic phenomena in any patient will fluctuate in an inverse relationship has implied the hypothesis that there exists within the patient some fixed quantum of disturbed psychic energy that is bound and fixed either by a psychosis or by a psychosomatic illness.

The literature on this subject is analyzed in detail and the conclusion reached that the evidence does not validate this formulation of an inverse relationship between psychosis and psychosomatic disease. An extensive clinical experiment with a large number of patients from Bellevue Hospital and from private practice is reported; this experiment also does not support the concept.

In this series, no consistent relationship between the occurrence of psychosis and psychosomatic disease was found to exist. It is recommended that the formulation of a simple inverse relationship between these two entities be abandoned. It is not validated by clinical evidence, it is based on an unsound theoretic approach, and it imposes a break in the active vigorous treatment of psychosomatic conditions. It is suggested that in its place an individualized approach should be substituted and awareness maintained that the important psychodynamic factors may be different in each patient. Treatment should be based on evaluation of the specific etiologic and dynamic factors that are uncovered in each patient. 28 references.—*Author's abstract.*

21. *Mental Disorder Associated with Thyroid Dysfunction.* IAN GREGORY, London, Ontario, Canada. Canad. M. A. J. *75*:489–492, Sept. 15, 1956.

This article contains case reports on 2 patients apparently having functional (schizophreniform) psychoses associated with thyroid dysfunction and a discussion of certain aspects of symptomatology, etiology, and management.

The first case recorded was that of a patient who had had a thyroidectomy and in whom signs of a paranoid schizophrenic reaction associated with hypothyroidism subsequently developed. Signs of mental abnormality were resolved with administration of thyroid but reappeared on two later occasions when the patient was not receiving adequate medication. The other case described a patient who was admitted to the hospital with a schizoaffective type of psychosis of acute onset and who, after the mental abnormality had improved considerably with psychiatric treatment, was found to have marked thyrotoxicosis, which was treated with radioactive iodine.

In analyzing the symptomatology of mental disorders secondary to thyroid dysfunction, it appears that primary signs of organic mental impairment are common in advanced

myxedema but rare in thyrotoxicosis. Secondary functional signs (due to release of latent tendencies) are common in both, particularly in thyrotoxicosis.

The etiologic relationship of thyroid dysfunction to mental disorder is complicated by observations that abnormal thyroid activity may be an effect as well as a cause of mental abnormality, or it may exist coincidentally. Evidence of a reciprocal relationship between thyroid and mental functions and certain aspects of the management of mental disorders associated with thyroid dysfunction are discussed.

It appears that primary hypothyroidism is predominantly somatopsychic in etiology, mental symptomatology, and treatment, whereas thyrotoxicosis is commonly regarded as psychosomatic in these respects.

The frequent association of mental abnormality with somatic disease necessitates an understanding of psychodynamics, as well as tissue pathology, a knowledge of both mental and physical symptomatology, and a comprehensive bio-psycho-social orientation toward investigation and therapy. 21 references.—*Author's abstract.*

22. *Reaction of the Adrenal Cortex to Emotional Stress.* EUGENE L. BLISS, CLAUDE J. MIGEON, C. H. HARDIN BRANCH, AND LEO T. SAMUELS, Salt Lake City, Utah. Psychosom. Med. *18*:56–76, Feb., 1956.

The authors investigated the influence of psychologic stress upon adrenocortical function and compared the changes in the 17-hydroxycorticosteroid level (compound F) in the plasma and urine found during emotional stress with those produced by other physical, chemical, and endocrine stresses as well as those obtained during normal, quiescent periods. In previous studies of 267 normal subjects, it was determined that the normal plasma 17-hydroxycorticosteroid level of these subjects at 8 a.m. was 13 μg., with a standard deviation of 6 μg. A normal diurnal rhythm was also identified.

Trends were consistent in both individual and group studies. The groups included emotionally disturbed patients admitted to a psychiatric unit, distraught relatives of patients seen in the emergency room of a hospital, medical students examined prior to crucial examinations, and patients about to receive electric shock treatments. As groups, all demonstrated elevated concentrations of plasma steroids with a mean value of 20 μg. and an increase of 7 μg. above normal values.

Individual longitudinal studies were made on neurotic and normal subjects and on persons in the manic phase of a manic-depressive psychosis. In these subjects, emotional perturbation was also associated with elevations in the level of the plasma 17-hydroxycorticosteroids. Urinary studies were less extensive, but they did show an increased urinary concentration of 17-hydroxycorticosteroids in conjunction with elevated plasma steroid values after emotional upset.

Experimental emotional stresses were induced by employment of dull, monotonous tasks, lysergic acid, stressful interviews, self-analysis before a one-way vision mirror, and the like. When subjects were separated into those who showed clear-cut affective changes and those who were relatively undisturbed, a significant steroid increase was evident in the group of emotionally disturbed persons.

It was concluded that emotional stress produces an elevation in the level of 17-hydroxycorticosteroids in the plasma and urine, indicating an increase in adrenocortical function.

However, the increases due to emotional upset are modest and are not as large as those caused by ACTH, a *Pseudomonas* polysaccharide, insulin, and electric shock. 42 references. 18 figures. 2 tables.—*Author's abstract.*

PSYCHIATRIC NURSING, SOCIAL WORK, AND MENTAL HYGIENE

23. *The Community and Rehabilitation of the Hospitalized Psychiatric Patient.* LUCY D. OZARIN, Washington, D. C. J.A.M.A. *161*:940–944, July 7, 1956.

The burden of mental illness, if only because of its magnitude, is shared by the entire American public. Mental illness is a challenge and a responsibility to the entire medical profession.

Psychiatric illness is often a chronic disease. Present-day psychiatric therapies are effective in many cases in abating the acutesymptoms. Hospitalized patients, when over the acute episode but still bearing residuals of the illness, often do not need to remain in the hospital. By means of rehabilitation, these patients, some of whom have been hospitalized for long periods, are able to return to the community and become independent citizens.

The transfer of a psychotic patient from a locked ward to an open ward in the hospital should be thought of as the first step back to community living. A number of methods have been devised to bridge the gap from hospital to community and to make the transition easier for the patient.

A trial visit or convalescent leave is the means by which most psychiatric patients leave the hospital, particularly the mental hospital. The patient lives in his own home or elsewhere and has the advantage of regular consultation and supervision by the hospital staff to ease his adjustment back into the community. For patients who have no suitable homes, arrangements can be made for placement in a home other than their own in which the patient becomes a member of a foster family. Data on the results of thousands of such placements are available.

Other plans are available to fit the needs of patients who no longer require hospital treatment but who still need help. These plans include day or night hospital arrangements whereby a patient may spend only the day or the night at the hospital, living at home or pursuing a vocation the remainder of the time. Various work placement plans have been devised with payment of salaries and independence to varying degrees in living arrangements in the hospital or in the community. Halfway houses have been utilized in which a patient lives in a type of residential club with professional consultation available while he is finding work and making permanent living arrangements. Sheltered workshops are a final step toward complete vocational rehabilitation.

Data are given on each of these plans and the results of the practices discussed. The experience of the Veterans Administration is used for illustration. Each plan fits only certain patients, and all these plans are successful only to the degree that a community accepts them and provides the facilities required for their success.

Physicians, by individual leadership and through medical society action, can help by educating the public regarding the needs of the mentally ill, and they can help in their personal contacts with psychiatric patients and their families. 7 references.—*Author's abstract.*

PSYCHOLOGIC METHODS

24. *Relationships Among Wechsler, Weigl, Rorschach, EEG Findings, and Abstract-Concrete Behavior in a Group of Normal Aged Subjects.* MARGARET THALER, Washington, D. C. J. Gerontol. *11*:404–409, Oct., 1956.

A group of 116 persons over 60 years of age were tested. They were living independently in the community and were deemed by examining physicians to be free of demonstrable cerebral defect, senility, arteriosclerotic disease, or functional psychoses. The intelligence quotient range was within normal limits, and the mean education level was above average for national expectancies for this age group. Yet extensive concreteness and literalness were found among the group.

Statistically significant relationships (1 per cent level of confidence) were found between higher scores on the Wechsler Intelligence Scale and more abstract performance on the sorting test, between associative impoverishment on the Rorschach and concrete behavior on sorting; 66 per cent of the group had concrete-literal methods for sorting objects. Sixty two per cent of the electroencephalograms were classed as abnormal; those persons with normal and focal records tended to attain higher scores on the psychologic tests than did those persons who gave mixed or diffuse tracings. Increasing age paralleled decreasing performance on the intelligence test.

Extensive concreteness and literalness was found among this group of supposedly normal older persons. These same persons had appeared alert and responsive in conversation spontaneously introduced by them. Yet they experienced great difficulty in performing examiner-initiated tasks, particularly in the area of forming concepts. The performance of these older persons suggested that those who functioned at concrete levels on the tests might also be concrete in other ways. They may try to adjust by sheer attempts to recognize aspects of their environment and be unable to form inferences and conceptually interpret what is happening around them. They may be literal in comprehending what is said to them and in their humor and jokes. They may feel there is only one meaning to a situation, may fail to see other meanings, and hence may have the "rigidity" so often attributed to older persons.

The large number of abnormalities found on the electroencephalograms of this group of supposedly normal older persons, their extensive concreteness and literalness, and other indications of impaired skills, suggest that capacity limitations may be a more pertinent way of viewing rigidity in older persons than solely studying set toward tasks among them. 18 references. 6 tables.—*Author's abstract.*

25. *Simple and Choice Reaction Time in Cerebral Disease.* HAROLD L. BLACKBURN AND ARTHUR L. BENTON, Iowa City, Iowa. Confinia neurol. *15*:327–338, 1956.

Two tests of visual reaction time (simple and choice) were administered to 30 hospitalized, nonpsychiatric patients on whom a firm diagnosis of supratentorial cerebral disease or injury was made and to 30 hospitalized, nonpsychiatric patients who had no evidence or history of cerebral disease or injury. The two groups of patients were closely comparable with respect to age, educational level, and proportion of men and women. Each patient

had normal (90 per cent) use of both upper extremities and sufficient vision to see both test lights at once with ease.

It was found that patients with brain damage were significantly slower than control subjects in both simple and choice reaction time. An appreciable proportion of these patients displayed longer reaction times than did the slowest control patient. With the simple reaction time procedure discrimination between the persons in the two groups was better than with the choice procedure. The results were interpreted as providing no support for the hypothesis that the degree of retardation is positively related to the complexity of the task. 14 references. 1 figure.—*Author's abstract.*

TREATMENT

b. Drug Therapies

26. *A Study of Chlorpromazine: Methodology and Results with Chronic Semidisturbed Schizophrenics.* ROBERT A. HALL AND DOROTHY J. DUNLAP, San Jose, Calif. J. Nerv. & Ment. Dis. *122*:301–314, Oct., 1955.

The present study was initiated to provide accessible, controlled, reproducible data regarding the effect of chlorpromazine on a sample of a fairly well-defined, reasonably homogeneous and clinically important group of patients and to study the problems of experimental design presented in setting up double blind controls with this and with similar drugs. Of 175 hospitalized patients who were semidisturbed chronic schizophrenics, 87 were given chlorpromazine and 88 a placebo. The drug and the placebo were given orally in tablet form; parenteral administration was employed only when the oral route was resisted. The starting dose of 25 mg. three times daily was increased every 3 to 10 days in 25 to 50 mg. steps until one of the following was reached: (1) 450 mg. daily administered without apparent therapeutic response; (2) a plateau of therapeutic response judged by reports of the nursing personnel; (3) toxic response calling for discontinuation or reduction of the dosage.

Results yielded evidence that chlorpromazine was significantly effective (at 5 per cent level) in inducing a slight but definite improvement in psychosis as evaluated by psychiatrists and a psychologist. Compared to the patients receiving a placebo, the group of patients receiving chlorpromazine showed no evidence of significantly greater improvement in behavior as rated in nine areas by psychiatric technicians on a modified Fergus Falls Scale. The control patients appeared to improve in 18 per cent of the cases as evaluated by a psychiatrist and psychologist and in striking degree in several areas of behavior as rated by technicians. The paranoid subtype showed the greatest response that can be attributed to the drug. The greater the initial tension as rated by the psychiatrist, the greater the response. Although expressions of delusions to technicians were significantly reduced, hallucinations were not, and there was no definite evidence that the basic psychotic process was altered by the drug. It was concluded that, although chlorpromazine has a useful action, it is principally that of a sedative and has little value for schizophrenic persons who are not tense, except possibly for those within the paranoid subtype.

The double blind method of this study broke down for the most part because of errors of design in the revealing nature of the side effects encountered. Nevertheless it is stressed that consideration of patients receiving drugs only would have led to spuriously impressive

results. The amount of improvement among control subjects re-emphasizes the need for carefully controlled studies and points to the potency of such factors as suggestibility on the part of patients and observers and improvement due to increased attention. It also emphasizes, once again, that human beings, chronically psychotic or not, are responsive to psychologic influences. The improvement in the control subjects would seem to document the need for more personnel and facilities to bring psychotherapy to the chronic wards of state hospitals. 17 references. 4 figures. 13 tables.—*Author's abstract.*

27. *Use of Megaphen in the Treatment of Psychoses* (*Erfahrungen mit Megaphen in der Behandlung psychisch Erkrankter*). ERHARD PHILLIP, Berlin, Germany. Nervenarzt *26*:59–65, Feb. 20, 1955.

Megaphen was used in the treatment of 159 patients with psychoses, 64 of whom were schizophrenics. Treatment was usually begun with a dosage of 75 to 100 mg. daily; after three days the dosage was increased to 150 to 200 mg. In some cases Megaphen was used without "shock" treatment; in other cases electroshock or insulin was employed, or a combination of the two. The results indicated that Megaphen had no direct effect upon any type of psychosis but had a favorable effect on certain symptoms, especially the relieving of anxiety and restlessness, and also in diminishing the incidence of hallucinations that in some cases disappeared entirely as long as the Megaphen treatment was continued. Megaphen may be considered to have a definitely favorable effect, although not curative, on various types of psychoses. 10 tables. 5 references.—*Author's abstract.*

28. *Complications of Chlorpromazine Therapy.* IRVIN M. COHEN, Galveston, Texas. Am. J. Psychiat. *113*:115–121, Aug., 1956.

The author describes the therapeutically undesirable effects of chlorpromazine encountered during a 14 month study of 1400 patients. Those occurring most frequently reflected direct or indirect action on various levels of the nervous system. Complications, presumably of allergic origin, were second in frequency. Two other categories of complications were distinguished, including presently unexplainable reactions such as excessive dreaming and indirect effects such as hypostatic pneumonia in elderly hypersomnolent patients. Included in the presentation is a discussion of the effects of chlorpromazine on the central nervous system and the cardiovascular, gastrointestinal, dermatologic, respiratory, musculoskeletal, endocrinologic, urinary, and hematologic effects.

Most of the complications that occurred during the first two weeks of treatment were of limited clinical significance. They were mainly central depressant, sympatholytic, parasympatholytic, and myatonic effects. The only alarming complication that appeared during this phase was acute circulatory insufficiency. Major complications were more likely to occur during the second two weeks of treatment, including jaundice and dermatologic reactions and disorganization of extrapyramidal motor regulation. The occurrence in 2 patients of syndromes resembling dystonia musculorum deformans indicated that parkinsonism was not the only extrapyramidal syndrome that could be induced by chlorpromazine. Other adverse effects were sensorium changes due to cerebral vascular hypotension, delirium, severe acute allergic reactions, and exaggeration of confusional effects of electroconvulsive

therapy. Leukopenia, leukocytosis, and eosinophilia occurred, but there were no cases of agranulocytosis.

No reliable standards were found by which a serious reaction could be predicted, although a history of allergy was of suggestive value. Fortunately even the most severe reactions were self-limiting, frequently resolving without reduction in dosage or discontinuation of the drug. The conclusion is reached that chlorpromazine has many undesirable effects but is clinically a relatively safe drug. 12 references.—*Author's abstract.*

For Reference

29. *Contribution to the Study of Reserpine in Psychiatry: Clinical and Electroencephalographic Results.* (*Contribution à l'étude de la réserpine en psychiatrie: résultats cliniques et électro-encéphalographiques.*) Ann. méd.-psychol. *114*:545–580, April, 1956.

c. Psychotherapy

30. *The Use of Chlorpromazine in Psychotherapy.* H. L. NEWBOLD AND W. DAVID STEED, Hines, Ill. J. Nerv. & Ment. Dis. *123*:270–274, March, 1956.

Since the advent of the clinical use of chlorpromazine in this country in 1954, many studies have been published comparing groups of treated and untreated cases. However, little has been done to study effects on the individual.

In this study, the authors chose 4 subjects already undergoing psychotherapy (a depressive reaction, a schizophrenic reaction, a schizo-affective schizophrenic reaction and a passive-aggressive personality). In a double-blind experiment the subjects were given increasing doses of chlorpromazine, that is, 50 mg. daily gradually increased to 400 mg. daily for 10 weeks. After having maintained the subjects on 400 mg. of chlorpromazine daily for four weeks, the medication was suddenly discontinued. Observations while the patient was undergoing psychotherapy showed that the medication had a marked tendency to mask emotional feelings.

The authors conclude that this masking effect was beneficial in psychotherapy as long as it helped reduce emotional feelings to the point where a meanful relationship could be established between the patient and the therapist.

The drug was judged harmful to the psychotherapeutic situation if it was given in sufficiently high dosage to reduce emotional feelings to the extent that the patient had no significant emotional feelings to express in psychotherapy. 11 references.—*Author's abstract.*

d. The "Shock" Therapies

31. *Deaths Following Electrotherapy: Report of Five Deaths, with Autopsy Findings in Four Cases.* SAUNDERS P. ALEXANDER, Orangeburg, N. Y., LAWRENCE H. GAHAGAN, AND WILLIAM H. LEWIS, JR., New York, N. Y. J. A. M. A. *161*:577–581, June 16, 1956.

Five deaths associated with electroconvulsive therapy occurred during a recent six year period at Rockland State Hospital, Orangeburg, N. Y., among 5325 patients, who received a total of about 70,000 treatments. This yielded a case fatality rate of 1 death/1065 patients and a treatment fatality rate of 1 death/14,000 treatments. Except for a marked skeletal deformity in 1 patient (a 57 year old man) and essential hypertension with blood pressure of

180/120 mm. of mercury in another patient (a 41 year old woman), all other observations on pretreatment examinations, including those by electrocardiography and chest radiographs, were within normal limits.

In 1 patient death followed the first treatment; in another patient death followed the fifty sixth treatment. In 4 the conventional (alternating current) technique was used; in the remaining patient, unidirectional current technique was used. In the case with the skeletal deformity (kyphoscoliosis), the treatment was modified by use of myoneural blockade with gallamine triethiodide.

In 4 of the 5 cases (all except in the patient with essential hypertension), autopsy was performed, and definite evidence of coronary artery disease or insufficiency was noted. In 1 patient (a 44 year old woman), the middle portion of the main branch of the left anterior coronary artery was completely occluded by fresh thrombus.

It is the authors' opinion that death during treatment is more commonly the result of a concatenation of factors, some chronic (such as coronary sclerosis), others acute or treatment-induced (such as cardiac rhythm disturbances, paroxysmal arterial and venous hypertension, hypoxia, and increased work of the heart). The main cause of death during treatment is the failure of the circulatory system to withstand the suddenly increased demands or the strain imposed at the time.

At present there is an inherent or hidden risk in treatment that cannot be eliminated because of the presence of undetected, or undetectable, coronary artery sclerosis or insufficiency and because of the effect of electric stimulation upon the impaired or inadequate coronary circulation. Treatment-induced strain on the cardiovascular apparatus may be lessened, however, through various modifying procedures and adjuvants among which are atropine, chlorpromazine, quinidine, tetraethylammonium and other autonomic ganglionic blocking agents, oxygen insufflation, myoneural blockade (particularly by succinylcholine), barbiturate anesthesia, digitalis preparations, and antihypertensive drugs. These modifiers are used as required for the safe management of the individual.

The authors conclude that despite cardiovascular complications (which are much more frequent in older persons) the case fatality rate in psychiatric electrotherapy is low; whenever treatment is indicated, this fact should as a rule outweigh other considerations, provided adequate precautions are taken. 13 references. 2 tables.—*Author's abstract.*

32. *Menstrual Disturbances During Electric Shock Treatment.* S. T. MICHAEL, New York, N. Y. Psychiatric Quart. *30*:63–72, Jan., 1956.

Electric convulsive treatment is accompanied by physiologic side effects that may hold clues to the mechanisms involved in the therapy. One of these side effects in women is menstrual disturbance, which has been shown statistically to go in the direction of amenorrhea and which is roughly proportional to the number of treatments. Characteristically significant changes occurred in the length of the menstrual cycle during which the shock treatment was begun. This menstrual cycle either became shorter, remained unchanged, or became lengthened, the latter being the most frequent.

The menstrual cycles of 331 patients treated in a hospital were studied in relation to clinical improvement and diagnostic category. Although the average menstrual cycle concurrent with inception of treatment was longer in patients who recovered (44.3 days) than

it was in patients who improved (40.9 days) and who did not improve (39.0 days), this difference was not statistically significant. The same relationship was found in a diagnostically and technically uniform subgroup of schizophrenic patients. Only four manic-depressive patients were classified other than recovered; therefore, analysis could not be applied to this group.

Even if clinical improvement was not correlated with the observed menstrual disturbances, several diagnostic categories were characterized by differences in response to shock treatment. Thus menstrual cycles in the groups of manic-depressive and paranoid patients treated by less than 10 treatments were short. In persons having psychoneuroses the menstrual cycles were only moderately lengthened, whereas the "nuclear," "constitutional" schizophrenic persons (all schizophrenic subjects excluding those in the paranoid group) usually had lengthened menstrual cycles following shock treatment. These differences in menstrual reactions were interpreted as due to a difference in the constitutional endocrine make-up of the patients in the different diagnostic categories. 7 references. 1 table.—*Author's abstract.*

33. *The Death Experience in Insulin Coma Therapy.* EILEEN WALKENSTEIN, New York, N. Y. Am. J. Psychiat. *112*:985–990, June, 1956.

Observation of patients undergoing insulin coma therapy who experienced feelings of dying with an associated stage III coma raised the question of a possible pathophysiologic basis of the death experience. This study, conducted at the Kingsbridge Veterans Administration Hospital, attempts to investigate the relationship between the depth of coma and the occurrence of the death experience. Ten patients described death feelings during insulin coma therapy in such words as the following: "I thought I was dead." "Everything seemed to be standing still." "I felt paralyzed and just came from the dead." "I struggled to come back to life; it was horrible." Of these 10, only 3 had stage III coma. There were 7 patients who suffered from one to six stage III comas, none of whom encountered the death experience.

A review of the literature indicates numerous theories for symptomatic improvement following the death experience during shock treatment. In this study it was found that 4 of 10 patients with death experiences showed no improvement; of 10 patients who suffered stage III coma, 4 showed no improvement. No positive relationship appeared to exist between the occurrence of either the death experience or the stage III coma and symptomatic improvement.

The results of this study may be subject to such criticisms as the small sampling of patients used, the occasional difficulty in accurately differentiating between stage II and III coma, the semantic problems encountered, and the reliance to some degree on the possible faulty memory of the patient.

The physiologic reaction of the human organism to shock treatment is discussed. It is speculated that any procedure involving a sudden death-facing shock to the organism may effect similar results to those obtained from the methods of shock treatment currently in use. Within the statistically limited scope of this study, it is concluded that no positive correlation exists between the occurrence of the death experience in insulin coma therapy and the depth of coma. 10 references. 1 table.—*Author's abstract.*

neurology

CLINICAL NEUROLOGY

34. *A Particular Variety of Headache.* SIR CHARLES SYMONDS, London, England. Brain *79*:217–232, June, 1956.

The analysis is presented of 17 patients who had attacks of severe pain in and around the eye after long intervals of freedom. The duration of the attack or paroxysm was seldom less than half an hour or more than two hours. The frequency of the paroxysms during an attack varied from less than one to eight in twenty-four hours. The duration of the attack was usually between two and eight weeks. Intervals of freedom lasted in most cases for more than six months and extended up to ten years. Fourteen of the patients were men, and the average age at onset was 27.

In the last 8 patients of the series, self-administered injections of ergotamine tartrate, timed so far as possible to anticipate the attacks, were successful in preventing them. The largest single dose recommended was 0.5 mg., with a total dosage of not more than 1.5 mg. in 24 hours. One patient, however, being a man in the medical profession, gave himself 0.5 mg. six times hourly for two weeks at the height of an attack without ill effect. This type of headache was first described by Wilfred Harris. It has subsequently been the subject of papers by Horton and others and is rightly considered to be a migrainous variant. Its clinical features merge with those of other syndromes. The justification for regarding it as a distinct clinical species is that, since the attacks are self-limited and seldom last more than eight or ten weeks, they can be treated by repeated injections of ergotamine tartrate without any harmful effects of a lasting nature.

The toxic symptoms that may result from the prolonged use of ergotamine tartrate are discussed with references to the literature and to cases observed by the author, and the conclusion is reached that if certain precautions are observed no harm is likely to result from administration of ergotamine tartrate in larger doses and over longer periods than those previously assumed to lie within the margin of safety. 17 references.—*Author's abstract.*

35. *Characteristics of Postural Tremor and in Various Abnormal States.* WALTER J. FRIEDLANDER, San Francisco, Calif. Neurology *6*:716–724, Oct., 1956.

In spite of the fact that it was demonstrated as early as 1896 that postural tremor occurs in normal persons, no mention of this normal phenomenon is made in most modern textbooks under the usual classification of tremor or in the majority of scientific papers on tremor. One is more often than not left with the impression that tremor in itself is an abnormal sign. Tremorgrams were obtained on approximately 700 patients who were referred for an electroencephalogram. A measurable postural tremor was demonstrated in 100 per cent of these. In normal persons, the frequency pattern varies from a very regular 8 to 12 per second pattern (looking much like printed alpha in an electroencephalogram) to one almost entirely made up of somewhat irregular 15 to 24 per second vibrations. In normal persons,

no correlation was evident between age and frequency, age and amplitude, or frequency and dominant hand; there was a suggestion that the faster frequency patterns tended to have lower amplitude. In serial tremorgrams on normal persons, there was some degree of constancy of the frequency pattern but not of the amplitude. The postural tremor seen in patients with anxiety states and for the most part the postural tremor seen in chronic alcoholic patients differed significantly from the normal postural tremor in amplitude only. Some patients with parkinsonism had a postural tremor indistinguishable from that of normal persons except for a greater amplitude. No statistically significant difference was found between the rate or the amplitude of the postural tremor in patients with postencephalitic parkinsonism and patients with paralysis agitans. Most of the patients with unilateral disease of the central nervous system had normal postural tremor; the most striking deviation from normal in this group was an alteration of rate with some slow and irregular vibrations. However, this difference was so inconstant that it was believed that the tremography, at least at this time, is of no specific value as a clinical diagnostic tool. 18 references. 7 figures. 1 table.—*Author's abstract.*

36. *Myasthenia Gravis with Features Resembling Muscular Dystrophy.* LEWIS P. ROWLAND AND ALFREDO N. ESKENAZI, New York, N. Y. Neurology *6*:667–671, Sept., 1956.

Myasthenia gravis has been regarded traditionally as a disease of the myoneural junction in which the muscles show no alterations other than the presence of small collections of lymphocytes. In recent years, however, the demonstration of significant alterations of the muscle fibers in some cases has suggested that the pathophysiology of myasthenia gravis may involve muscle as well as, or instead of, the neuromyal junction.

To illustrate this, a case is reported of a woman who had had prominent weakness of the extremities from the time she first began to walk. She had never been able to move her eyes as long as her parents could remember, but they could not recall whether or not this difficulty had been present during the first year of life. When she was examined at the age of 37, several features suggested that she had muscular dystrophy, namely, creatinuria, tissue changes noted on histologic examination, and weakness predominantly in the shoulder, pelvic girdles and trunk that resulted in a waddling gait, lordosis and an inability to rise from the supine or sitting positions. However, she had no marked wasting or contractures. There was almost complete ophthalmoplegia and bilateral ptosis of the eyelids. The deep reflexes were preserved. The patient responded dramatically to neostigmine and ed-rophonium chloride (Tensilon) and demonstrated exquisite sensitivity to curare, thus establishing the presence of myasthenia gravis. 19 references. 3 figures.—*Author's abstract.*

37. *Hyperinsulin Neuronopathy.* DONALD W. MULDER, JAMES A. BASTRON AND EDWARD H. LAMBERT, Rochester, Minn. Neurology *6*:627–635, Sept., 1956.

A syndrome of distal muscular atrophy and paresthesia associated with hyperinsulinism has been observed in 20 patients. Hyperfunctioning adenomas of the islet cells of the pancreas were demonstrated as the cause of hyperinsulinism in 18 patients. These symptoms of distal muscular atrophy and paresthesias began after severe episodes of hypoglycemia and tended to persist for months and even years after the hyperinsulinism had been cured.

Others have reported the occurrence of a similar syndrome following injection of excessive amounts of insulin in insulin-coma therapy and during treatment for diabetes. In the patients included in this report the distal muscular atrophies and paresthesias seemed directly related to hyperinsulinism. These symptoms began during severe episodes of hypoglycemia, the presence of hyperfunctioning adenoma of the pancreas caused progression of the symptoms, and the removal of the adenoma arrested the progress of the atrophy and paresthesia.

It is postulated that the pathophysiology of this syndrome involves both the anterior horn cells and the peripheral nerves. The authors suggest that this syndrome might best be described as hyperinsulin neuronopathy. The differentiation of this syndrome from progressive muscular atrophy, peroneal muscular atrophy, and chronic neuronitis is discussed. It is suggested that hyperinsulin neuronopathy may account for some of the neuropathies seen in diabetic patients. 19 references.—*Author's abstract.*

38. *Neuromuscular Problems in Hemiplegic and Paraplegic Patients.* LENOX D. BAKER, Durham, N. C. Geriatrics *11*:434–439, Oct., 1956.

As new discoveries and scientific contributions prolong the life of man, new therapies and wider use of old procedures will be needed for care of the aged. This article emphasizes the importance of surgical correction of deformities in the hemiplegic and paraplegic patient. A description is given of the use of various neuromuscular surgical procedures, particularly tenotomies, tendon transplants, partial neurectomies, and joint stabilizations, that may contribute to the rehabilitation of these patients who, if they become ambulatory, can resume self-care and often can fill a useful place in industry and society. The surgical procedures described are directed at restoration of muscle balance and establishment of control of the joint for better function.

39. *Neurologic Signs and Symptoms as a Prodrome to Virus Hepatitis.* WALTER J. FRIEDLANDER, San Francisco, Calif. Neurology *6*:574–579, Aug., 1956.

In a series of 185 consecutive cases of viral hepatitis (infectious hepatitis and homologous serum jaundice), were 1 patient with definite neurologic signs and symptoms before the onset of jaundice, 2 patients with questionable neurologic involvement before jaundice, and 2 patients with neurologic involvement coinciding with the onset of jaundice. The patient who had definite neurologic involvement was a 60 year old man who had at the onset right abducens paralysis, questionable right trigeminal nerve involvement, and increased deep muscle reflexes on the left appearing seven days before the onset of jaundice. These neurologic signs disappeared in two to three weeks.

A review of the literature would indicate that neurologic signs and symptoms are rare in viral hepatitis. Of a total of 8167 cases of patients with viral hepatitis and homologous serum jaundice, which were reported because of hepatitis and not merely because of the neurologic signs and symptoms, 0.2 per cent of the patients had neurologic signs and symptoms before the onset of icterus. Thirty-one incidences of neurologic signs and symptoms before the onset of jaundice have been culled from the literature. Nineteen incidences of meningitic, 14 of encephalitic, 9 of neuritic, and 5 of myelitic involvement were noted. The

onset of neurologic signs and symptoms in persons with infectious hepatitis varied from 2 to 18 days before the jaundice appeared, with an average of six days; the time interval between the appearance of neurologic signs and symptoms and the onset of jaundice in 3 persons with homologous serum jaundice was 72 days, 56 days, and 1 day. Spinal fluid findings were normal in about half the cases; mild increases in pressure, total protein, and/or cells characterize the other half.

The prognosis in general is good even if the patients are profoundly ill; residual neurologic signs and symptoms, however, have been reported. The differential diagnosis should include infectious mononucleosis and viral hepatitis plus some other concomitant disease such as poliomyelitis. 56 references. 1 table.—*Author's abstract.*

ANATOMY AND PHYSIOLOGY OF THE NERVOUS SYSTEM

40. *Studies in Itching. II. Some Psychological Implications of the Interrelationships Between the Cutaneous Pain and Touch Systems.* JOSEPH G. KEPECS AND MILTON ROBIN, Chicago, Ill. Arch. Neurol. & Psychiat. *76*:325–340, Sept., 1956.

When the skin is lightly stroked with cotton wool for two minutes, several types of subjective responses appear, namely, (1) normal adaptation in which sometime within the test period an initial sensation of itch or tickle is replaced by touch; (2) no adaptation in which tickle or itch only are perceived during the test period; (3) touch throughout; (4) shifting adaptation in which responses tend to alternate between tickle and touch; and (5) partial adaptation in which there is a diminution, but not complete disappearance, of itch or tickle sensations during the test period.

A pilot study of a number of patients with various dermatoses indicated that emotionally labile patients tended to show no adaptation, whereas more controlled persons showed normal adaptation.

Five patients with various dermatoses were studied while hospitalized, and their reactions to cotton stroking were compared with their personality structures, transference attitudes, and state of dermatoses. The authors observed that those patients in whom transference responses tended to be of the all-or-nothing type, namely, either excessively defensive or excessively, ill-controllably emotional, generally showed all-or-nothing skin responses—either all itch-tickle or all touch. As the dermatoses improved, the all-itch responses became touch-only responses. Patients in whom the affects were better integrated and less polar showed more skin responses of normal adaptation. As the dermatoses improved, tickle-only responses changed to normal adaptation. A patient showing marked emotional volatility, with some attempts at control, vacillated between itch-tickle and touch sensations, exhibiting shifting adaptation.

By and large, the more severe the emotional constriction and the more intrapunitive the patient, the more responses of itch rather than of tickle were elicited. This seems to be connected with the fact that itch is closer to the pain end of the pleasure-pain spectrum than is tickle.

The pain-pleasure series (pain, itch, tickle) is closely related to erotic instinctual life. The touch system is related to and subserves ego functioning. Responses of normal adaptation appear related to optimum balance between erotic, instinctual life, and ego control,

insofar as this can be reflected in the skin. Reactions of no adaptation (all itch or tickle) indicates excessive emotionality and deficient control. Touch-only reactions are correlated with attempts at excessive and rigid control or affects. 18 references. 4 figures. 8 tables. —*Author's abstract.*

For Reference

41. *On the Correlation Between the Function and Structure of Nerve Cells.* G. VRAA-JENSEN. Acta psychiat. et neurol., Scandinav. suppl. *109*:1–88, 1956.

CONVULSIVE DISORDERS

42. *Diurnal Rhythm in Epilepsy.* MAX LEVIN, New York, N. Y. Am. J. Psychiat. *113*: 243–245, Sept., 1956.

Epileptic seizures do not occur at random throughout the day and night. On the contrary, mass statistics show a peak incidence at certain hours, specifically the last hours of sleep and the first few hours after waking in the morning. Moreover, there are persons in whom most or even all of the seizures occur during these hours. The reason for this peak would appear to lie in the interplay of inhibition and excitation. Epilepsy is due to a discharging lesion, and the seizure results from excitation. A great daily cycle of excitation and inhibition occurs. The excitation potential of the brain is exhausted at the end of the day, at which time activity is suspended and the subject sleeps, that is, inhibition takes over. During sleep the brain recovers and, when the excitation potential has been restored, the subject wakes, ready for another day. This could explain why seizures are more likely to occur in the hours just before and after waking. It would not explain why in a few persons seizures occur by preference in the early hours of sleep. 10 references.—*Author's abstract.*

43. *Hibicon in Treatment of Epileptics with Mental Disorder.* SIDNEY MERLIS AND DONALD W. MARTIN, Central Islip, N. Y. Psychiatric Quart. *30*:386–401, July, 1956.

Eighteen patients with previously severe uncontrolled convulsive disorders and concomitant psychic disorders received a therapeutic trial with N-benzyl-B-chlorpropionamide. Of these patients, 16 improved, 14 showed definite improvement in the psychic sphere, and 16 showed definite improvement in the convulsive sphere. Side effects were minimal. Five cases are presented to demonstrate the clinical responses of the patients.

It is concluded that N-benzyl-B-chlorpropionamide, if given alone or in conjunction with other standard anticonvulsants, will often produce definite beneficial effects in the psychotic epileptic person. 5 references. 1 figure. 2 tables.—*Author's abstract.*

DEGENERATIVE DISEASES OF THE NERVOUS SYSTEM

44. *Multiocular Encephalomalacia.* W. KRAMER, Heemstede, Holland. J. Neurol., Neurosurg. & Psychiat. *19*:209–216, August, 1956.

The brains of two patients who died at the age of 21 months and 8 years, respectively are described. In both brains multiple small cavities were found. The microscopic picture of the hemispheres of the younger child showed an enormous overgrowth of glial tissue and

rests of immature cells. The changes bore much resemblance to the cyst-like changes in bone or the growth of a congenital cyst of the liver or kidney. That the growing process is to be compared with a benign tumor was supported by the clinical progress. It was supposed that dishistogenesis started during embryonic development as the result of a familial predisposition to degeneration of the central nervous system; 2 uncles and 4 cousins of the father had spinocerebellar disease. The mechanism by which the cysts developed is discussed. In the second patient the cyst was confined to the white matter. This and the cortex were transformed into a dense net of glia cells with signs of proliferation. Immature cells were found in the neighborhood of the ependyma and around the blood vessels in the white matter. It was supposed that toxemia of the mother had damaged the brain of the child, the remnants of the matrix of the neopallium having the ability to proliferate. The mother had similar toxemia during her second pregnancy that led to the birth of a defective child. The brain of this child had been previously described by the author as "poliodysplasia cerebri." Unlike the elder sister, disordered histogenesis had led to underdevelopment of both the neurons and glia cells in all parts of the brain. 84 references. 11 figures. 2 tables.—*Author's abstract.*

45. *Infantile Encephalomalacia with Multiple Cavity Formation.* BERNARD J. ALPERS, RODNEY A. FARMER, AND H. EDWARD YASKIN, Philadelphia, Pa. Arch. Neurol. & Psychiat. *76*:229–235, Sept., 1956.

Sporadic reports of encephalomalacia with cavity formation in infants have appeared in the literature. This report is added to the increasing number of such reports, which the authors believe have resulted in an increasing recognition of the condition as a disease entity. In this report another case is described and the pathologic aspects elaborated upon.

Infantile encephalomalacia in an infant three and a half months old was characterized by numerous cystic areas in both grey and white matter of the brain and in the region of the basal ganglia, and by sparing brainstem and cerebellum. Microscopic study revealed pia-arachnoid thickening, profuse gitter cell accumulation with cyst formation, frequent focal glitter cell collections, calcium deposits in some of the areas of necrosis, and areas of only partial destruction of tissue. The blood vessels were on the whole intact, but endothelial swelling was sometimes present and often the perivascular spaces were filled with macrophages and mononuclear cells.

The features recorded in this case correspond well with those previously reported. Variations in the location and extent of the lesions have occurred from patient to patient. The outstanding variations described here consisted of extensive involvement of both grey and white matter. The pathogenesis is not clear. 7 references. 6 figures.—*Author's abstract.*

DISEASES AND INJURIES OF THE SPINAL CORD AND PERIPHERAL NERVES

46. *Extradural Spinal-Cord Hematoma: Report of a Case Due to Dicumarol and Review of the Literature.* DONALD B. ALDERMAN, New Haven, Conn. New England J. Med. *255*:839–842, Nov. 1, 1956.

A case of spinal cord extradural hematoma in a patient receiving bishydroxycoumarin

(Dicumarol) is presented. This syndrome masqueraded as lumbosacral strain until neurologic signs and subcutaneous ecchymoses appeared.

Fourteen well documented cases of extradural hematoma of the spinal cord previously reported in the literature are reviewed. This is the third case recorded in which the condition was ascribed to bishydroxycoumarin toxicity. This diagnosis should be entertained for any patient receiving anticoagulants in whom low back or sciatic pain develops.

The use of spinal tap and simplified ethyl iodophenylundecylate myelography established the diagnosis in the case reported here. Surgery, although only partially successful, was followed by considerable improvement. Earlier intervention might have yielded better results.

The need for frequent prothrombin time determinations is emphasized. Repeated examinations of the urinary sediment for red cells in patients receiving bishydroxycoumarin seem indicated. 24 references. 2 figures.—*Author's abstract.*

ELECTROENCEPHALOGRAPHY

47. *The Value of the Electroencephalogram in Selected Cases of Subdural Hematoma.* RICHARD C. TURRELL, LEWIS L. LEVY, AND EPHRAIM ROSEMAN, Louisville, Ky. J. Neurosurg. *13*: 449–454, Sept., 1956.

Twelve cases of unilateral subdural hematomas in adults are presented in which the unique finding of ipsilateral hemiparesis was noted, that is, hemiparesis on the side on which the subdural hematoma was located. The electroencephalograms showed a reduction in amplitude and a delta wave focus on the side on which the subdural hematoma was located.

The report stresses that (given the criteria of a person in coma with or without a history of head injury) in the presence of reduction of amplitude and slow wave focus on the same side as the focal neurologic signs, suspicion of the possible existence of an extracerebral lesion such as a subdural hematoma should be strong.

Evidence is given that the amplitude asymmetry shows up in some epochs better than in others, and the best combination is one in which symmetric areas are triangulated.

In spite of an improving electroencephalogram, from the standpoint of disappearance of generalized delta activity, persistence of ipsilateral reduction in amplitude and slow wave focus in a person who has had a head injury points strongly to the possible existence of a subdural hematoma on the side of the amplitude reduction. 3 references. 3 figures.—*Author's abstract.*

48. *Electroencephalography in Somnambulism and Its Value in Establishing an Etiologic Diagnosis. (L'électroencéphalographie dans le somnambulisme et sa valeur pour l'établissement d'un diagnostic étiologique.)* G. ANDRÉ-BALISAUX AND R. GONSETTE, Bruxelles and Charleroi, Belgium. Acta neurol. et psychiat. belg. *56*:270–281, April, 1956.

After reviewing 150 electroencephalograms of men from 19 to 25 years of age who gave a history of somnambulism, the authors ruled out 50 patients because of inconclusive information or because the symptoms could not be checked during hospitalization.

Study of clinical and electroencephalographic data of the 100 other cases led to classification into three groups. In Group I the patients had infrequent, benign spells, the family

and personal histories revealed nothing pertinent and the electroencephalograms were normal. In Group II, between spells the patients had hyperemotivity and the electroencephalograms showed cortical hyperexcitability. In Group III the patients had severe somnambulism, and many had a family history of the same disorder as well as a personal history of infection or trauma of the central nervous system during childhood. Electroencephalograms show marked alterations.

The authors agree with the conclusions of Passouant who recommends treating the patients of Group III with anti-epileptic drugs, such as phenylacetylurea. 20 figures. 5 tables.—*Author's abstract.*

49. *Electroencephalographic Study of Insufficiency of the Basilar and Carotid Arteries in Man.* JOHN S. MEYER, HERBERT LEIDERMAN AND D. DENNY-BROWN, Boston, Mass. Neurology 6:455–477, July, 1956.

Thirty-six patients with recurrent cerebrovascular symptoms due to severe insufficiency of the internal carotid or basilar arteries have been studied in terms of the electroencephalogram, the electrocardiogram, and blood pressure recordings. Any clinical manifestations such as high blood pressure were lowered by a tilt table or carotid compression.

Data were obtained relating to changes in blood pressure and pulse with postural tilt in 24 healthy medical students, whose average age was 23. In the larger group suffering from cerebrovascular disease, the diagnosis was confirmed at autopsy in 4 and by arteriogram or surgery in an additional 10. In the remaining patients diagnosis was based on clinical signs and symptoms.

For control purposes the electroencephalogram has been studied in relation to postural tilt and carotid compression in 7 healthy boys, in 5 young adults who had undergone surgical ligation or who had proved occlusion of a main cerebral vessel without recurrent symptoms, in 20 older patients with miscellaneous diseases excluding cerebrovascular insufficiency, and in 11 with a diagnosis of syncope of various types. Postural tilt to 70 degrees produced no clinical signs or symptoms in any of the patients with basilar artery insufficiency. In 2 of the patients with occlusion of one carotid artery, clinical signs and symptoms appeared; in both there was syncope and in 1 a short focal seizure occurred. Carotid compression, however, produced signs in a larger proportion of the cases studied. In 1 patient with basilar artery insufficiency, carotid compression reproduced an attack similar to the complaints. Carotid compression caused focal or generalized seizures in 7 of the 23 patients with carotid insufficiency.

In basilar or carotid insufficiency the fall in both systolic and diastolic blood pressure with postural tilt was found to be significantly increased compared to that of the persons in the control group. In the control study no change occurred in the electroencephalogram by postural tilt to 70 degrees in the group of young or older persons or in those with miscellaneous neurologic conditions including the presenile and senile dementias but excluding those with degenerative vascular disease of the brain. Carotid compression is a much less specific test. With this maneuver focal electroencephalogram changes developed in 1 of the young healthy control subjects, and diffuse slowing developed in 1 young patient with a surgically ligated carotid artery.

Of 36 patients with occlusion of the anterior, middle, and posterior cerebral arteries by vascular disease, or with multiple small scattered infarcts, the procedure was of relatively little value, 13 showing a poorly defined accentuation of a resting abnormality. In the group of 11 patients with a clinical diagnosis of syncope of various types, 5 showed electroencephalographic patterns compatible with carotid artery insufficiency; most of these were diagnosed as postural syncope.

Fall in blood pressure were demonstrated to give rise to electroencephalographic changes consistent with transient focal cerebral ischemia in the distribution of the affected vessel. If the degree of insufficiency is more severe because another major cerebral vessel is diseased, the electroencephalographic abnormality appears in the distribution of both the affected vessels. For example, the postural electroencephalographic abnormality in basilar insufficiency complicated by disease of the carotid arteries may result initially in bursts of slow waves in the distribution of one or both posterior cerebral arteries and then spread forward to the sylvian areas.

The degree of cerebrovascular insufficiency must be advanced before postural changes appear in the electroencephalogram. Thus in 5 young patients having undergone surgical ligations of either one vertebral, carotid, or middle cerebral artery there was no accentuation of an electroencephalographic abnormality with postural change, presumably because of the excellent collateral circulation in young persons and the absence of severe postural changes in blood pressure. For this reason, it is doubtful that the method is of much value in evaluating patients for neurosurgery prior to ligation of a carotid artery, although the method could be made more stressful by administering hypotensive agents prior to the test. However, this technique could be dangerous in patients with severe cerebrovascular insufficiency. Electroencephalographic changes in the patients studied in this group frequently appeared within 8 to 15 seconds of carotid compression or repeated tilts. Such short latency suggests local neuronal hypoxia as the cause.

These studies show that, in the presence of insufficiency of the carotid and basilar arteries, an induced fall in blood pressure averaging 43/19 mm. of mercury may give rise to a focal abnormality that can be the basis of episodic syncope, dizziness, confusion, dementia, and seizures. The combination of cerebrovascular disease and heart disease results in serious liability to postural ischemia of the brain. 41 references. 10 figures.—*Author's abstract.*

INFECTIOUS AND TOXIC DISEASES OF THE NERVOUS SYSTEM

50. *Does Virus Encephalitis Cause Mental Defect?* HAROLD BOURNE, Otago, New Zealand. Am. J. Ment. Deficiency, *61*:198–209, July, 1956.

After tabulating for many years the clinical material for severely mentally defective children at a large and busy hospital, it was concluded that most cases ascribed to encephalitis are, in fact, examples of a syndrome termed acute epileptic dementia, which usually but not always occurs without pre-existing epilepsy.

The cases that can be convincingly attributed to virus encephalitis are so much below 1 per cent as to be a negligible factor in the problem of mental deficiency. It seems likely that virus encephalitis is overrated in textbooks as a cause of mental defect. 8 references. 2 tables.—*Author's abstract.*

INTRACRANIAL TUMORS

51. *The Natural History of Intracranial Neoplasms.* MARTIN G. NETSKY AND JAMES MACD. WATSON, Winston-Salem, N. C., and New York, N. Y., Ann. Int. Med. *45*:275–284, August, 1956.

Usually intracranial neoplasms have a gradual onset and a progressively deteriorating course. This is in contrast to the rapid onset, quick progression, and later recession of signs in persons having sustained cerebrovascular accidents. Six cases of persons with tumors of the brain are presented in which sudden onset and recovery from signs and symptoms were noted, in some instances more than once. The neoplasms included glioblastoma multiforme, malignant lymphoma, astrocytoma, oligodendroglioma and meningioma. The course in each case is graphically illustrated, and the pathogenesis of sudden onset and intermittent symptoms discussed. It is concluded that herniation of various portions of the brain and cerebral edema and swelling are the more likely causes. Hemorrhage into a neoplasm is uncommon and the role of vasospasm is uncertain at the present. The possibility of variation in the rate of growth of intracranial neoplasms is considered. The prediction of the natural history of the disease by histologic diagnosis may be valid statistically, but the range of variation is wide and the prognosis offered may not be valid for the individual. It is pointed out that awareness of any type of tumor of the brain is diminished when the onset is apoplectic, especially when remissions occur. The cases cited demonstrate that recession of signs and symptoms is not a conclusive argument against diagnosis of intracranial neoplasm. Recovery of the patient should not, therefore, cause the clinician to relax his consciousness of neoplasm. 15 references. 2 figures.—*Author's abstract.*

52. *Alteration of Consciousness: Tumor of the Reticular Activating System.* N. L. MASON-BROWNE, Essondale, B. C., Canada. Arch. Neurol. & Psychiat. *76*:380–387, Oct., 1956.

The cortex has long been held to mediate consciousness. More recently it has been postulated that the diffuse projection system of the brain stem may be responsible for crude consciousness. The case reported is that of a 41 year old woman. During the two years preceding admission cardinal signs were episodic disturbances of consciousness. An epidermoid cyst of the third ventricle was incompletely removed at operation. The patient continued in a state of akinetic mutism episodically for some time, and death occurred seven months later. At autopsy no herniation of the brain stem and no evidence of hydrocephalus or of pressure on the cortex was found. During the patient's lifetime no indication that the symptoms were due to cerebral anoxia was noted; the symptoms must, therefore, have been caused by the local effects of the tumor of the brain stem. It is known that such signs as were predominant in this patient need not have been produced by interference with the ascending and descending tracts. Thus the presumption is reasonable that disordered function of the reticular activating system was responsible, although the mechanism remains unestablished. Cairns has established that destructive lesions in the anterior part of the third ventricle produce, variously, stuporous states and fits of various types, including petit mal-like fits, and in one case produced a condition resembling catatonic schizophrenia. A

single case is reported of a destructive lesion involving the rostral brain stem that produced gross impairment of consciousness as its cardinal sign. The case confirms the fact that somewhere within the brain stem lies a mechanism intimately concerned with the maintenance of consciousness. It is accepted that no conclusions can be drawn from a single case, but it is confirmed and emphasized that destructive lesions to the brain stem produce states closely akin to many psychotic conditions in which alterations of consciousness are involved, the causation of which remains obscure. Speculation is made that certain psychotic states may be due to disturbances of the brain stem reticular system. 28 references. 1 figure. —*Author's abstract.*

53. *Intracranial Tumors Found at Autopsy in Mental Patients.* ROY B. PATTON AND JOHN A. SHEPPARD, Tacoma and Fort Steilacoom, Wash. Am. J. Psychiat. *113*:319–324, Oct., 1956.

The authors report the kind and incidence of intracranial tumors found at 2,161 autopsies performed in a large mental hospital. The literature is cited, and the kind and incidence of intracranial tumors found at autopsy in mental and non-mental hospitals is compared. Statistically these figures indicate that intracranial tumors are more common in patients who had had mental disorders. Various factors that may account for this are discussed. The most important of these may be that meningiomas were much more frequently found in patients who had had mental disorders. Several persons have noted the tendency of the slow growing meningiomas to produce psychiatric symptoms. This could account for the increased number of meningiomas found at autopsies in mental hospitals.

The kinds of tumors found in this study are compared with those found in similar studies. Each group is then discussed with particular attention given to metastatic tumors. The spread of these tumors to the intracranial cavity is discussed, as are meningiomas, which produce psychiatric symptoms, frequently the only manifestations of the condition. 32 references. 5 tables.—*Author's abstract.*

54. *Pseudotumor Cerebri: Benign Intracranial Hypertension.* LEO M. DAVIDOFF, New York, N. Y. Neurology *6*:605–615, Sept., 1956.

Pseudotumor cerebri is defined as a syndrome of increased intracranial pressure producing headache and papilledema and as a condition that is usually without other neurologic manifestations. The cerebrospinal fluid is under increased pressure but shows a normal total protein content and normal cell count. The pneumoencephalograms are within normal limits, without dilatation, deformity, or displacement of the ventricular system. This paper is based on the author's personal experience with 61 cases.

The treatment in all cases is aimed at relieving intracranial hypertension. In mild cases this can be done by limitation of fluid intake and promotion of water excretion alone. In patients with more severe papilledema, subtemporal decompression should be done first, followed by the afore-mentioned measures.

The prognosis in the majority of cases is excellent, although many months or even several years may be required for the condition to subside completely. 18 references. 4 tables.—*Author's abstract.*

NEUROPATHOLOGY

55. *Relation of Chlorpromazine to Epilepsy.* A. F. MESZAROS AND P. O. O'REILLY, North Battleford, Saskatchewan, Canada. Dis. Nerv. System *17*:159–162, May, 1956.

The literature on the clinical effect of chlorpromazine was surveyed and compared with the authors' own material. It appears that chlorpromazine has epileptogenic properties that may manifest seizures in susceptible people. On the other hand, an epileptic disorder is favorably influenced by chlorpromazine. Ten institutionalized epileptic patients were given chlorpromazine combined with anticonvulsant medication for 10 months. There was a marked decrease of irritability, hostility, and aggressive and destructive outbursts. Seizures during treatment with chlorpromazine occurred in 6 patients. The seizures were confined to the early period of treatment, namely, from the first day to the third or fourth week of treatment. Seizures were less likely to develop if previous anticonvulsant medication was continued. Electroencephalographic records showed a decrease of fast activity, and the alpha waves were more prominent than those obtained prior to chlorpromazine treatment. There was no improvement regarding the epileptic activity in the records.

The results suggest that chlorpromazine tends to decrease the seizure threshold; this action is possibly counterbalanced by potentiating the effect of anticonvulsants and by decreasing the level of tension. The reduction of tension is probably due to the depressant effects on the bulbo-meso-diencephalic reticular system. This action would counteract the triggering of seizures by affective stimulation. The improvement of behavior does not depend on changes in the epileptic activity. On the other hand, amelioration of electroencephalographic signs of tension appears to be a significant concomitant of improved behavior. 25 references.—*Author's abstract.*

TREATMENT

56. *Parsidol in the Treatment of Parkinson's Syndrome.* ITSURO SOBUE AND ELINOR R. IVES, Nagoya, Japan, and Los Angeles, Calif. Bull. Los Angeles Neurol. Soc. *21*: 80–83, June, 1956.

Thirty-one patients with Parkinson's syndrome were studied in the Los Angeles County Hospital neurology outpatient clinic to evaluate the effect of Parsidol [N-(2-diethylaminopropl) phenothiazine hydrochloride]. Twenty-two men and 9 women were studied 14 of whom were between 40 and 50 years of age. The remainder were over 50. Encephalitis accounted for 8, and trauma possibly accounted for 2. The duration of symptoms ranged from 1 to 28 years, with half of the patients having suffered for over 10 years. Ten cases were classified as mild, 20 as moderate, and 1 as severe. Results were determined by subjective and objective criteria of ability to perform certain exercises and tasks. Five patients showed good improvement and 12 slight improvement. Of these was a lessening of both tremor and muscular rigidity. Oculogyric crises were controlled in 1 patient and decreased in frequency in another. Cerebration seemed facilitated in some. Parsidol proved most effective in the postencephalitic patients, with 6 out of 8 improved, compared to 11 of the 23 others.

Agranulocytosis occurred in 2 patients. In both, the leukocyte count returned to normal after the drug was stopped. Twenty-four of the 31 patients complained of dryness of the mouth, dizziness, nausea, tiredness, weakness, drowsiness, blurred vision, staggering gait, flushed face, numb fingers, itching ears, or increase in symptoms. About one-third of the patients stopped taking Parsidol because of unfavorable reactions. When the drug was continued or temporarily withheld and then resumed in smaller doses, symptoms disappeared or did not recur. Patients exhibited a marked difference in tolerance to the drug. Parsidol should be begun in small doses and gradually increased to not more than 600 mg. daily. 9 references. 1 table.—*Author's abstract.*

57. *Parkinson's Disease: Aspects of Functional Training.* WILLIAM A. MURRAY, Long Island, N. Y. Physical Therap. *36*:587–594, Sept., 1956.

The family of the patient who has Parkinson's disease requires orientation in order to know how to supply the necessary assistance to the afflicted member. Too frequently it is found that the patient begins to expect and eventually receives more aid than is required or therapeutically desirable.

The aim of physical therapy is to reduce and retard the development of the secondary changes at the musculoskeletal level produced by lesions of the basal ganglia. Procedures designed to increase joint range of motion and motor power are basic to re-training of the patient in self care and ambulation. Exploiting the physical environment of the patient's home is invaluable toward setting up both self-treatment opportunities and minimizing the patient's obstacles.

Studying the patient's motor dysfunction should be a continuing practice. Approaching the subject's problems very often must be on a trial and error basis. A number of methods derived in this way are discussed in their application to ambulation, bed, chair, and feeding activities. 16 references. 1 figure.—*Author's abstract.*

BOOK REVIEWS

Problems of Consciousness: Transactions of the Fifth Conference. HAROLD A. ABRAMSON, Editor. New York, N. Y., Josiah Macy, Jr. Foundation, 1955. 180 pp. $3.50.

This book is a report on the final conference on the problems of consciousness sponsored by the Josiah Macy, Jr. Foundation. The purpose of the conferences is to recognize the hidden obstructions to communication between workers in different professional fields and to foster a cross discipline approach to problems. Twenty-two members are listed as participants in the five conferences. Thirteen members and 2 guests were present at this conference. Of the 8 absentees, 7 were psychiatrists or psychologists.

Four discussions are reported: Three Dimensions of Emotion, Anxiety, The Role of the Cerebral Cortex in the Development and Maintenance of Consciousness, and Aesthetics. In the opinion of this reviewer the most valuable part of the book is the discussion on anxiety led by Dr. Roy Grinker. To a greater extent than is usual in conference reports the participants succeed in communicating with the reader as well as each other.

It is obvious that some members had reservations about accepting consciousness as a

suitable subject for scientific investigation. However, some progress appears to have been made in combatting this point of view.—*Margaret Mercer, Ph.D.*

Educating Spastic Children. ELEANOR F. SCHONELL. New York, N. Y., Philosophical Library, 1956. 242 pp. $6.00.

The stated purpose of this book is "to provide first-hand information of an educational and psychological kind for all concerned with the education, upbringing and general welfare of the cerebral palsied." It is written in four parts with the first part devoted to a brief, nontechnical discussion of the nature of cerebral palsy and a review of the development of resources for treatment in the United States, Australia, and Great Britain. The second part is a report of a medical and psychological survey of cases of cerebral palsy among children of the West Midland area of England. This survey was sponsored by the Department of Paediatrics and Child Health at the Children's Hospital, University of Birmingham, and was done by Dr. Schonell, a psychologist, and Dr. Patria Asher, a physician. The third part deals with the factors determining the most suitable form of education for the child with cerebral palsy including a description of the Carlson House Experimental School for Spastics, Birmingham, England. Finally, the fourth part is devoted to a general discussion of the psychology of these children with some consideration of the problem of counselling parents.

It may be succinctly stated that the author achieves her purpose. Although the section concerned with reporting the results of her survey becomes tedious at times, the other parts amply atone for this. Particularly informative are the chapters devoted to the establishment of educational curricula and the special problems encountered, which should be very useful for the teacher of children with cerebral palsy. Parents of the child with cerebral palsy have a great deal to gain in terms of a better understanding of the emotional problems that face their child and, more important, of the role that they themselves play. The interested layman who simply wants to know more about a subject that has been cloaked in misconception too long will find this a fine survey of the problem. Finally, no reader can help being impressed by what can and has been done for a large percentage of the victims of this disorder, which was considered hopeless a few short years ago.—*Melvin Zax, Ph.D.*

Motivation and Personality. A. H. MASLOW. New York, N. Y., Harper & Brothers, 1954. 411 + xiv pp. $4.50.

This book enthusiastically presents a theory of human motivation and personality dynamics which appears to be based primarily upon the author's belief that there are certain basic psychologic needs such as self-esteem that are instinctive. The author develops his theme with the crusading spirit of one who finds that existing concepts of human nature are too pessimistic, limited, and atomistic to provide an understanding of man's inner nature and individual potentialities.

Except for the last three chapters, all of the material in this book has previously appeared in articles published by the author during the past 15 years. As a consequence, some of the content, as the author points out, is rather dated. This is particularly true of chapter

3, Holistic-Dynamic Theory in the Study of Personality, which attempts to resolve differences between experimental, clinical, atomistic, and holistic psychology. The first two chapters emphasize the importance of the scientist in science. About half of the volume is devoted to arguments favoring the author's theory of motivation, the role of basic need gratification, the instinctoid nature of these "basic" needs, the importance of threat to the instinctoid needs in psychopathogenesis, and a rejection of aggressiveness as instinctual. The author's chief argument for his instinctoid need hypothesis is that in his opinion, a noninstinctual approach to personality dynamics has failed. To support his thesis, the author points to various clinical observations of an interesting but vague nature. His arbitrary designation of certain psychologic needs as basic seems highly questionable.

The remainder of the book presents many worthwhile personal observations, particularly concerning love in "self-actualized" people and psychotherapy as a good human relationship. The author's style is refreshing.—*Albert D. Annis, Ph.D.*

Doctor and Patient and the Law. LOUIS J. REGAN. Ed. 3, St. Louis, Mo. C. V. Mosby Co., 1956. 716 pp. $12.50.

We welcome the appearance of this edition of a useful volume but regret to record the recent death of the author. Dr. Regan's volumes have done much to make clear to physicians their liabilities and their rights; in this task the author was greatly aided by having had both medical and legal training. Particularly did he emphasize the prophylactic aspects of the problem: how the physician can best avoid malpractice and other suits.

The material is well and clearly arranged and presented under such general headings as Malpractice, Physician and Patient, Liability for Act of Another, Expert Witnesses, Evidence, and Proof. Several new chapters have been added on the Public Health Law, the Grievance Committee and Malpractice, and the Patient's Interest in Malpractice.

There are voluminous references to cases; the index (by states) of cases comprises 72 pages. There is also a full topical index.

The volume is one that should be studied by every physician.—*Winfred Overholser, M.D.*

NOTES AND ANNOUNCEMENTS

Fifty Years of Psychology at Saint Elizabeths

On April 20, 1957, Saint Elizabeths Hospital in Washington, D. C., will hold a semicentennial celebration of the establishment of its first psychologic laboratory. In the Hospital's annual report for 1907 the superintendent, Dr. William A. White wrote, "The establishment of a psychological department in this hospital is an expression of the most advanced trends in modern psychiatry . . . and from present indications the psychological laboratory will in the future be considered as much of a necessity in connection with the asylum or psychiatric clinic as the pathological laboratory was formerly. . . . The opening of this laboratory is a step towards the creation here of a strictly scientific department for the study of mental diseases." The present occasion fittingly marks the official reopening of an experimental psychologic laboratory. The program highlights the transition from the physiologic laboratory approach to the modern dynamic clinical methods as exemplified by the history of fifty years of psychology at Saint Elizabeths.